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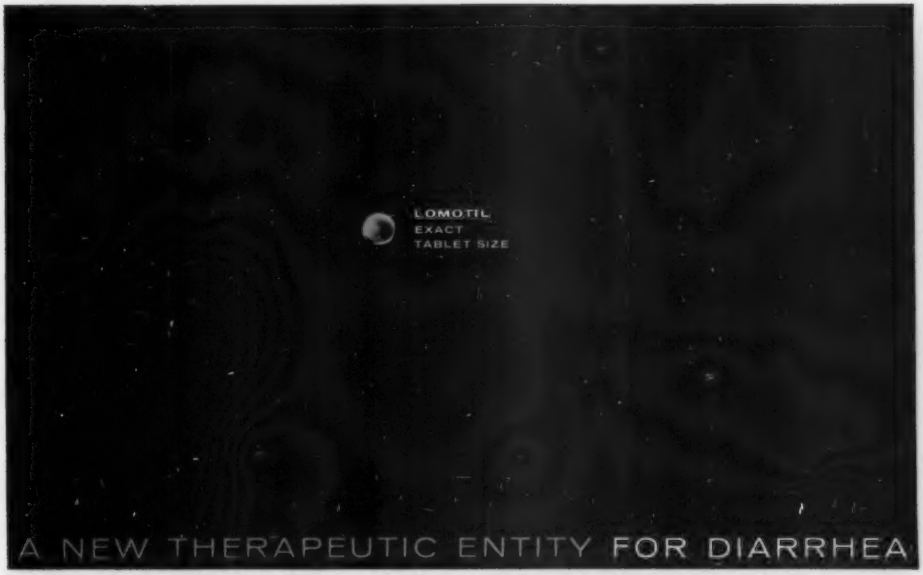

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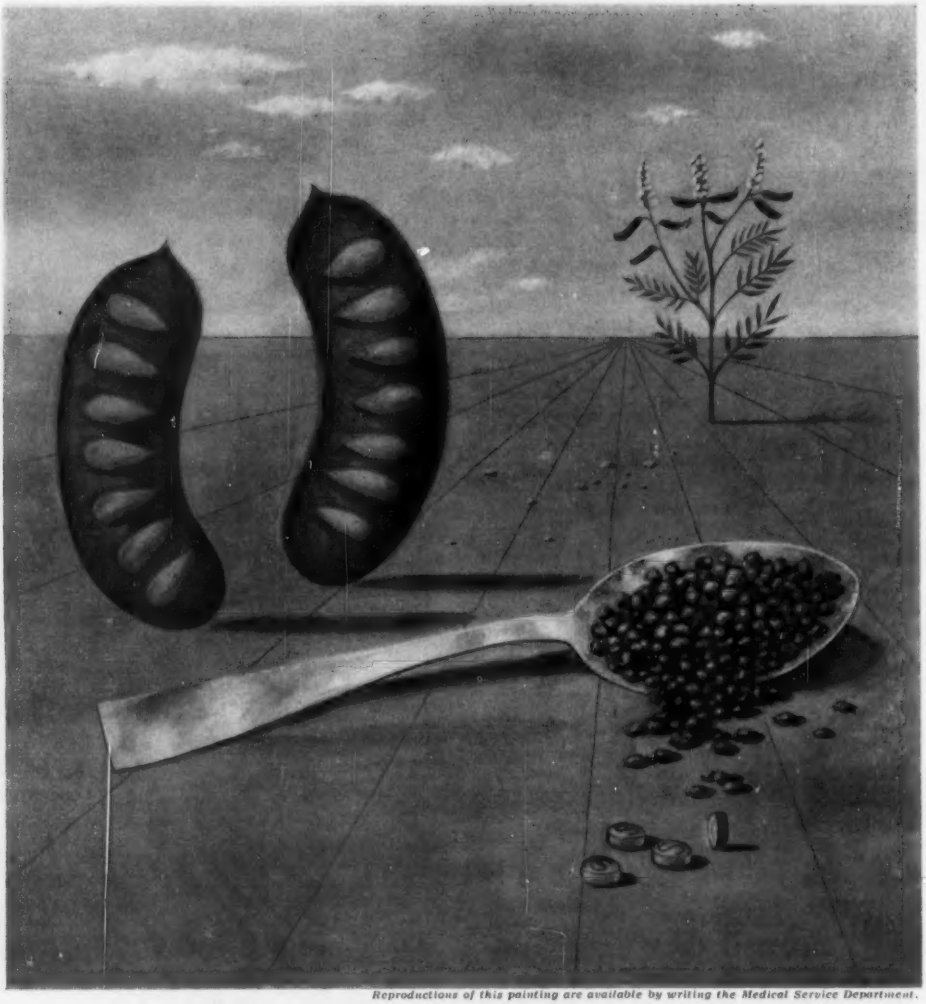

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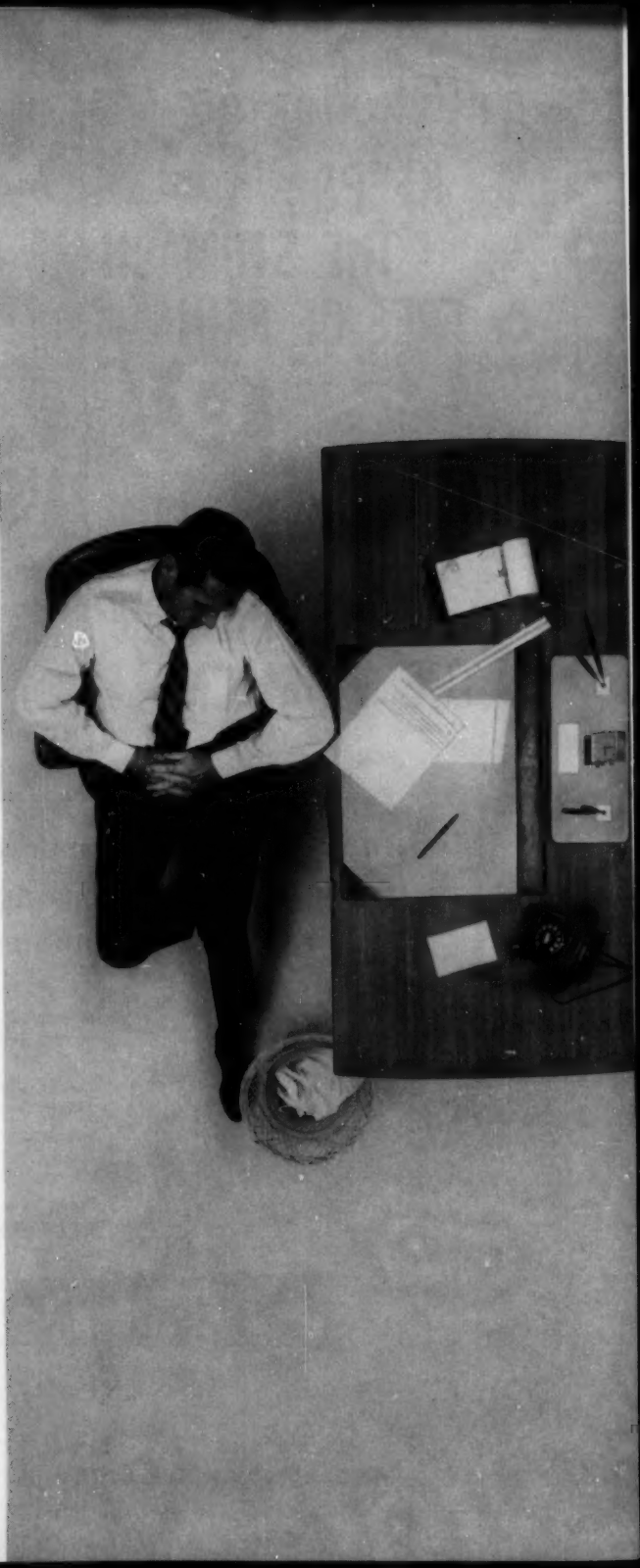

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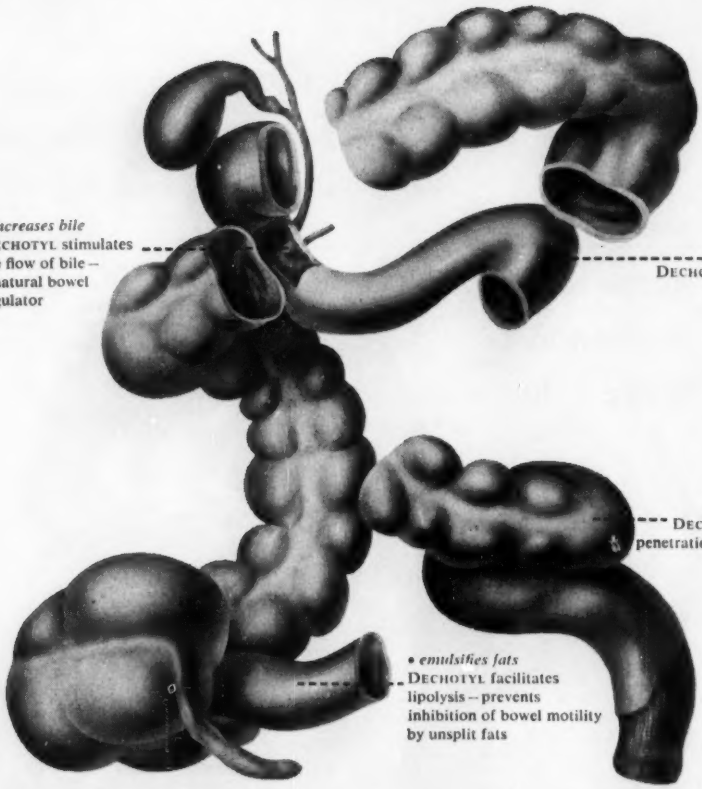

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SERUM TRYPSIN INHIBITORS IN THE NORMAL AND IN PATIENTS WITH ACUTE PANCREATITIS*

BARBARA DYCE

and

BERNARD J. HAVERBACK, M.D.

Los Angeles, Calif.

A number of investigators have demonstrated the presence of substances in serum which inhibit the proteolytic effect of trypsin. Camus and Gley[1] demonstrated this effect in 1897. Shulman[2] established the existence of two trypsin inhibitors by differential titration of human serum, and he also noted that one of the inhibitors (which accounted for about ten per cent of the total inhibitor) was also inhibitory to plasmin. Jacobsson[3], using zone electrophoresis, demonstrated that the inhibitors traveled with the alpha-1 and alpha-2 globulin fractions. More recently, Bundy and Mehl[4], using a modification of the Kunitz casein method, have determined that there is sufficient inhibitor in one milliliter of normal serum to neutralize 1.03 ($\pm$ 0.13) mg. of crystalline trypsin. Biologic fluids other than serum also have been shown to contain trypsin inhibitor. Shulman reported the presence of at least two inhibitors in urine; Laskowski[5] demonstrated trypsin inhibition by colostrum. Kunitz[6] and Grossman[7] have established the existence of trypsin inhibitor in the pancreatic juice of animals.

Ascoli and Bezzola[8], and Brieger and Trebing[9], found increased levels of trypsin inhibitor in the serum of patients with various diseases and, more recently Shulman[10], and Peacock and Sheeney[11], have shown the highest values of total trypsin inhibitor to be found in patients with tissue destruction. The increase in total inhibitor was reportedly found to be due to an increased

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From the University of Southern California School of Medicine and The Los Angeles County Hospital, Los Angeles, Calif.

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alpha-1 inhibitor. Patients with nephrosis differ in that they exhibit an increased alpha-2 component and a decreased alpha-1 component[12].

The purpose of this study was to determine: 1. the fractions of serum separated by electrophoresis, which inhibit trypsin, 2. the levels of serum trypsin inhibitors which occur in patients with acute pancreatitis.

Methods and Materials

Measurement of trypsin:—Proteolytic activity of trypsin was measured using the synthetic substrate benzoyl-l-arginine-paranitroanilide (BAPNA)[13]. Trypsin splits the substrate to yield benzoyl-l-arginine amide and the yellow dye, paranitroanilide.

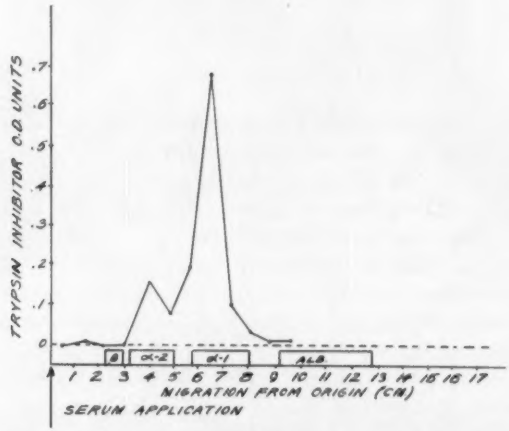

Fig. 1—Trypsin inhibitors in normal serum separated by electrophoresis. Protein fractions from one centimeter sections of the electrophoretic paper strip are eluted in tris buffer and assayed for trypsin inhibitory activity. Note that the larger portion of serum trypsin inhibitor migrates with the alpha-1 globulin and that a smaller amount migrates with the alpha-2 globulin.

In a 3.0 ml. BAPNA system, trypsin activity measured in Beckman O.D. Units per minute at 383 mu is directly proportional to the amount of trypsin added. When the change in optical density per minute is recorded, trypsin can be accurately assayed in the range of 1.0 mcg. To increase the sensitivity, trypsin was incubated with BAPNA and buffer for five minutes or longer, and the reaction stopped by the addition of 1 ml. of 0.2 N HCl. The total increase in optical density compared to blanks can accurately assay trypsin in the range of 0.5 mcg.

The following substances were used in this study:

1. Benzoylarginine-paranitroanilide (BAPNA) is synthetized by heating an equal molar mixture of paranitroaniline hydrochloride and benzoylarginine-amide in an oil bath to 150 degrees centrigrade. The mixture is kept at this temperature for five minutes after melting occurs. After cooling, the meld is washed repeatedly with 95 per cent ethanol to remove excess paranitroaniline; the mixture is then filtered and dried in a dessicator.

2. A supersaturated aqueous solution of BAPNA in a concentration of 1 mg. per ml. is prepared by heating to 85 degrees centrigrade until dissolution is complete and cooling in an ice bath. The solution may be stored at room temperature for at least one month without appreciable degradation.

3. 0.1 M Tris (hydroxymethyl) aminoethane buffer pH 7.67.

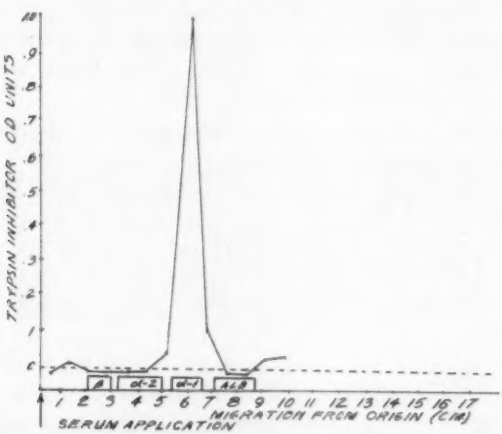

Fig. 2—Serum trypsin inhibitors separated by electrophoresis in a patient with acute pancreatitis. Note that the alpha-1 globulin trypsin inhibitor is higher than normal and that the alpha-2 globulin trypsin inhibitor is absent.

4. Trypsin standards. Lyophilized crystalline trypsin (Worthington Biochemical Corporation) was used. A stock standard of trypsin in a concentration of 1 mg. per ml. is prepared in 0.0025 N HCl. Working standard solutions of trypsin were prepared by diluting the stock standards to the desired concentration. Protein content of trypsin standards were determined by measuring at 280 mu in the Beckman DU Spectrophotometer and using the conversion factor of 0.585 as described by Kunitz[14].

Electrophoretic separation of serum:—Duplicate serum samples, in amounts of 50 or 100 lambdas, were applied to filter paper strips (Whatman 3 mm.) and the protein fractions separated electrophoretically in the Spinco Model R paper electrophoresis cell. Veronal Buffer, pH 8.6 (0.075 ionic strength) was used

and the system allowed to run (20 to 24 hours at approximately 150 volts and 15 milliamperes). The strips were removed and one stained with Bromphenol Blue dye for protein localization. The other strip was then cut into one centimeter sections and eluted over night in 1.5 ml. of tris buffer (0.1 M pH 7.67).

Inhibitor assay:—One and two-tenths ml. of the eluate from each centimeter section (except in the alpha-1 region where high inhibitor levels permitted the use of smaller quantities) was incubated for five minutes with the trypsin standard and then the residual trypsin was assayed, using the BAPNA substrate. After a ten-minute incubation period the lysis of the substrate was stopped by the addition of 1.0 ml. of 0.2 N HCl and the optical density recorded.

Results

The total trypsin inhibitor of nine normal sera using the benzoylarginine-paranitroanilide method had a mean level of 1.15± (0.10) mg. of crystalline trypsin inhibited per ml. of serum.

The components of serum proteins separated by electrophoresis which contained trypsin inhibitory activity were the alpha-1 and alpha-2 globulin fractions. None of the other fractions had inhibitory activity. All of the protein components were assayed for tryptic activity and none contained any significant amount. A typical normal trypsin inhibitor pattern is illustrated in Fig. 1. It will be noted that the alpha-1 globulin fraction contains approximately 90 per cent of the total inhibitory activity and the alpha-2 globulin component the small remainder.

Preliminary studies of the serum globulin trypsin inhibitor components in acute pancreatitis have indicated that there is a considerable increase in the alpha-1 globulin inhibitor and a decrease in the alpha-2 globulin inhibitor. In many cases of severe acute pancreatitis there was a virtual disappearance of the alpha-2 globulin inhibitor. As the alpha-1 globulin inhibitor increased in these patients, the ratio of alpha-1 globulin inhibitor to the alpha-2 globulin inhibitor became markedly elevated (Fig. 2).

Comment

The values for trypsin inhibitor in normal unfractionated serum using the substrate benzoylarginine-paranitroanilide are in close agreement with those reported in the study by Bundy where casein was used as the trypsin substrate. Use of the synthetic substrate, however, decreased the time required for the determination and provides an assay procedure which is at least as accurate and as sensitive as that using casein. Another advantage that is not pertinent to the reported study is the specificity of the synthetic substrate for trypsin, whereas trypsin, chymotrypsin, elastase, collagenase, and carboxypeptidase have a proteolytic effect on casein.

In agreement with previously reported studies, the larger share of serum trypsin inhibitor travels electrophoretically with the alpha-1 globulin and approximately ten per cent travels with the alpha-2 globulin. It is known that in many diseases of unrelated etiology that frequently the level of total serum trypsin inhibitor is increased. This increase, therefore, is not specific for acute pancreatitis. Also, it is likely that an increase in the total serum trypsin inhibitor which reflects the increase in the alpha-1 globulin trypsin inhibitor is no more specific in the various diseases than a sedimentation rate. The studies reported herein, however, indicate that in acute pancreatitis the alpha-2 globulin inhibitor decreases and in severe pancreatitis it may disappear. The divergent changes of the two serum globulin trypsin inhibitors in acute pancreatitis brings about a marked increase in the ratio of alpha-1 globulin inhibitor to alpha-2 globulin inhibitor. The specificity of the decrease in the alpha-2 globulin inhibitor for acute pancreatitis is presently being investigated. If the decrease is specific, the marked rise in the ratio of the inhibitors may well be a valuable diagnostic tool for acute pancreatitis.

Summary

1. Using the substrate benzoylarginine-paranitroanilide for trypsin assay, the level of total serum trypsin inhibitor in normal serum has been found to be 1.15± (0.10) mg. of crystalline trypsin inhibited per ml. of serum. Serum trypsin inhibitor can be separated into two components by electrophoresis. The component in greater amount travels with the alpha-1 globulin fraction comprising about 90 per cent of the total. The smaller component travels with the alpha-2 globulin fraction.

2. In acute pancreatitis, there is a marked increase in the alpha-1 globulin trypsin inhibitor and a decrease in the alpha-2 globulin trypsin inhibitor. In severe pancreatitis, the alpha-2 globulin trypsin inhibitor may disappear.

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PANCREATITIS AND RENAL INSUFFICIENCY

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The recent occurrence in our hospital of three cases of acute pancreatitis complicated by renal insufficiency with uniform fatal results prompted a review of the recent literature concerning this combination.

We hoped to find the answer how best to evaluate elevated serum amylase and lipase in renal failure; how to recognize and treat this type of irreversible shock.

The following cases have four factors in common: hemorrhagic pancreatitis, renal insufficiency, shock and death.

Case 1:—A 58-year old colored male was transferred to Cottage Hospital on 20 November 1959 after being treated seven days in another hospital. He was confused, lethargic and unable to give a history other than noting a history of urethral stricture, a recent urinary tract infection and a four-day history of dizziness. Physical examination revealed shock, confusion, moderate dehydration and right upper quadrant tenderness. His urine output was 60 c.c. per 24 hours. Laboratory data showed: serum amylase, 1,029 Somogyi units; serum sodium, 120 mEq./l; serum potassium, 7.5 mEq./l; serum chloride, 69 mEq./l; carbon dioxide combining power, 10.8 mm./l; hematocrit, 46 per cent; NPN, 202 mg. per cent and white blood count of 14,500. The ECG was normal. As we were unable to evaluate the elevated serum amylase in the face of the azotemia, a peritoneal aspiration was performed and was negative for fluid. He was treated in the usual conservative manner for acute renal failure until 22 November when the patient began to deteriorate, becoming confused and in deeper shock. The laboratory data was as follows: carbon dioxide combining power, 7.7 mm./l; serum chloride, 91 mEq./l; serum potassium, 6.4 mEq./l; NPN, 128 mg. per cent; serum sodium, 130 mEq./l; hemoglobin, 11.4 gm. and white blood count 26,000 cu.mm. On that day dialysis was performed with the Kolff twin coil artificial kidney for 4½ hours. Following this the patient was clinically improved, was out of shock and fairly alert. On 23 November there were 1,600 c.c. urine per 24 hours. On 24 November, after appearing satisfactory in the morning, he again became shocky, disoriented and developed icteric sclerae. The laboratory data was: NPN, 160 mg. per cent; serum sodium, 145 mEq./l; serum potassium, 6.5 mEq./l; serum chloride, 93 mEq./l and white blood count 43,000.

As a last resort, because we did not know the pathogenesis of his uremia or the cause of the abdominal pain, though pancreatitis was suspected, he was subjected to three hours of dialysis with the Kolff twin coil kidney without

improvement. The jaundice deepened, shock became unresponsive so the patient was returned to his room and he died one and one-half hours later.

Necropsy findings were: stricture of urethra, hydroureteronephrosis right, with chronic pyelonephritis right, congenital hypoplasia of left kidney and acute pancreatitis with retroperitoneal and intraabdominal hemorrhage.

Case 2:—A 64-year old white male with recent history of gallbladder surgery and pancreatitis was admitted to Cottage Hospital on 27 January 1959 following an auto wreck. He had multiple facial lacerations, a cold right leg with absent pulsation below the right knee, a generalized tender and distended abdomen. The serum amylase was 833 Somogyi units on 29 January and 800 Somogyi units on the next day. Hemorrhagic fluid aspirated from abdominal cavity showed an amylase of 714 Somogyi units. On 2 February carbon dioxide combining power was 21.9 mm./l; serum chloride, 98 mEq./l; serum potassium, 4.8 mEq./l; NPN, 102 mg. per cent and serum sodium, 146 mEq./l. The urine output was 115 c.c. on 31 January and 240 c.c. on 1 February. Because of the clinical deterioration of the patient, intermittent peritoneal dialysis was started on 1 February using the technic described by Grollman. This was continued for 28 hours, followed by a marked improvement in the patient's condition and an increase in urine flow to 1,380 c.c. on 6 February. On 7 February the patient again began to deteriorate. The carbon dioxide combining power was 11 mEq./l. and NPN was 152 mg. per cent. The urine volume decreased to 180 c.c. and patient went into shock. Intermittent peritoneal dialysis was again instituted and continued until the patient died at 3 A.M. on 8 February.

Necropsy findings were: acute pancreatitis with peripancreatic fat necrosis superimposed on chronic pancreatitis; acute tubular necrosis; gangrene of right leg due to embolus right femoral artery; acute erosive esophagitis.

Case 3:—A 58-year old white male was admitted to Cottage Hospital on 21 January 1960 for aortic graft surgery. An aortogram revealed a thrombus extending from the level of the renal arteries to the iliac arteries. The surgery was performed on 25 January under venovenal hypothermia with central temperature of 30° C. Except for technical difficulties with the left limb of the graft the patient tolerated surgery well. There was great difficulty with aortic dissection due to periaortic fibrosis. Following surgery the urine output decreased to 80 c.c. on 27 January. He experienced left chest pain, fever, tachycardia and shock. He was treated in the accepted manner for tubular necrosis. On 30 January the urine output was 60 c.c., the carbon dioxide combining power was 11.4 mEq./l; serum sodium, 137 mEq./l; NPN, 152 mg. per cent; serum chloride, 88 mEq./l; serum potassium, 5.5 mEq./l. The clinical condition steadily deteriorated despite steroid therapy, norepinephrine, heparin, antibiotics and blood transfusions. In an attempt to halt the metabolic acidosis and shock on 30 January dialysis using the Kolff twin coil artificial kidney with regional heparinization was commenced. There was no improvement after three-

hour dialysis and due to hemorrhage from the left limb of the graft the dialysis was discontinued. The shock was not responsive to norepinephrine or blood transfusions and the patient died.

Necropsy showed severe arteriosclerosis and organized thrombosis of abdominal aorta and iliac arteries, dacron bifurcation graft of lower abdominal aorta and iliac arteries, acute tubular necrosis, postoperative acute hemorrhagic pancreatitis and healed periaortic fibrosis, etiology not determined.

It is to be noted that the irreversible shock which developed in the above patients appeared while these patients were under accurate careful conservative therapy for acute tubular necrosis. When deterioration appeared vasopressor agents, antibiotics, blood transfusions and steroid therapy were added or increased without apparent success.

Serum amylase increases as a result of obstruction to exocrine outflow from the pancreas or parotid gland or if renal disease delays the amylase clearance. The amylase may be elevated in pancreatitis, parotiditis, peritonitis, renal insufficiency, mesenteric thrombosis, cholecystitis or penetrating peptic ulcer.

When renal insufficiency is present with acute pancreatitis, neither the serum or urinary amylase gives reliable information[1]. Meroney reported six cases of acute tubular necrosis showing elevated amylase without demonstrable pancreatitis and noted that the elevated amylase may return towards normal without the oliguria being relieved[2]. It has been demonstrated that lipase, like amylase, depends on renal function for elimination[3]. Following dialysis, there is no characteristic change in the elevated serum amylase. The dialyzing membrane filters out substances usually filtered by the glomerulus which suggests the renal excretion of amylase is by means other than glomerular filtration[4].

From the above statements we see that in the face of renal insufficiency, elevated serum amylase or lipase assumes no diagnostic implications. The presence of pancreatitis in this situation may be suggested by history and physical examination. Peritoneal aspiration as done in Case 1 to evaluate an elevated amylase was not helpful, though it was significant in Case 2.

Pancreatitis is a serious disease. Three-fourths of the cases remain in the edematous stage with a 5 per cent mortality; 15 per cent progress to acute hemorrhagic state with a 75 per cent mortality and 10 per cent progress to acute suppurative stage with a 25 per cent mortality[5]. Reid suggests that pancreatic necrosis is the result of vascular lesions with loss of cell membranes and escape of enzymes, not trypsin or chymotrypsin, which destroy any organ that is metabolically active at this time. Propylthiouracil, by inhibiting oxidative energy and depressing glandular activity, has been found beneficial in preventing pancreatic necrosis in the experimental animal[6]. Dragstedt states that most fatal cases of acute pancreatitis are due to extensive necrosis of the pan-

creas by trauma or interference with blood supply when the pancreas was actively secreting. He cited evidence suggesting bacteria, normally present in the body, elaborating fractions which are very toxic when absorbed[7]. In experimental animals epinephrine and related substances were found to convert mild interstitial pancreatitis into necrosis[8].

Beisel et al, found that acute renal failure is not an infrequent complication of acute hemorrhagic pancreatitis. They reported five cases, all of whom died, and suggested that pancreatitis with associated azotemia and oliguria, which is not responsive to hydration and correction of shock, be also treated as acute renal insufficiency. They also found this combination to have a grave prognosis[9].

The major cause of death in acute renal failure is cardiac arrhythmia or congestive failure[10]. The mortality averages 50 per cent but varies with the etiology of the acute tubular necrosis. In two recent surveys Kiley and Bluemle found 8 to 29 per cent mortality, respectively, in that of hemolytic or postpartum origin; a mortality of 65 to 72 per cent, respectively, in the group following postoperative or posttraumatic episodes[11,12]. Bluemle found infection to be the most common complication and it played a part in 72 per cent of deaths[12].

The early diagnosis of renal failure often must be made on criteria other than urine volume or retention of nitrogenous products in the blood. It may exist with minimal oliguria, normal urine volume, even polyuria. The blood urea may be high with or without renal failure under catabolic conditions, or the blood urea may be slow to rise in renal failure not associated with these conditions[13].

The cause of shock which preceded death in the three cases described, despite use of all accepted modalities to combat this event, was not clinically apparent. Whether acute hemorrhagic pancreatitis and renal insufficiency represent two serious diseases superimposed, with the expected high mortality, or whether the treatment of one aggravated the clinical course of the other is not clear at this time.

The most feasible cause of this shock is that of bacteriemia with production of endotoxins. For a complete review of this subject, the following articles are suggested:

Hall found in shock due to bacteriemia the signs of bacteriemia may not be apparent. The shock is the result of pooling of blood in the peripheral vessels despite vasoconstriction in the skin of the extremities. The genitourinary tract was the source of bacteriemia in 40 per cent of his cases, and the gram negative enteric bacteria caused the hypotension in two-thirds of his cases. He noted also that antibiotics controlled the bacteriemia but shock was not relieved; blood and plasma raised the blood pressure but did not seem to relieve the fatality rate; and steroid hormones did not appear to lessen the shock but vasopressor agents were useful[14].

Fine states that traumatic shock, however produced, becomes unresponsive to therapy when the "endotoxin detoxifying potential" of the reticuloendothelial system is destroyed. The refractory state of the peripheral vessels is due to unneutralized endotoxins which seem to magnify the local action of epinephrine and norepinephrine. This may be prevented by Reserpine and Dibenamine if given prophylactically[15]. Some of the local and systemic reactions to unneutralized endotoxins may be the altered reactivity of terminal blood vessels as, experimentally, endotoxins can produce hemorrhagic necrosis[16]. Thomas states that no single action of endotoxins can explain the shock but that it is the result of interlocking reactions and the sequence of events is as important as the events themselves in determining the final outcome.

Summary

Three cases of acute hemorrhagic pancreatitis with renal insufficiency were reported. The difficulty of evaluating an elevated serum amylase in the presence of renal failure was discussed. In retrospect, it seems as if shock due to bacterial endotoxins best explains the fatal shock in the above cases. Whether the early use of propylthiouracil to prevent pancreatic necrosis or the prophylactic use of Reserpine and Dibenamine to prevent the refractory state of small vessels or the earlier use of steroids to prevent the initial shock of bacterial endotoxins will prove clinically useful remains to be seen.

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CIRRHOSIS IN YOUNG WOMEN

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A rather significant number of cases of cirrhosis in young women, not apparently due to alcoholism or nutritional deficiency, have been noted in the past. Although a relationship to previous attacks of infectious hepatitis has been established in some, the etiological factor or factors involved in many of these cases has not been established. It is the purpose of this paper to present a case which typifies this problem and to discuss briefly the available information which relates to it.

A 24-year old white female was admitted to the hospital on 13 March 1957 for evaluation of liver disease. Four years previously she had excess bleeding following tonsillectomy. No transfusions were required, however. One week later she developed edema of the feet and ankles and was hospitalized with a diagnosis of rheumatic fever. There were no other symptoms at that time; the edema subsided following two weeks of bed rest.

One year later she noticed excessive bleeding of the gums; she was examined elsewhere at that time and told she had "slight jaundice" and an enlarged liver and spleen. In 1956 she developed generalized edema with ascites, pleural effusion and tarry stools. X-ray examination is said to have shown esophageal varices. Splenectomy was apparently considered but not performed.

A heart murmur was found at age 13. Menarche was at age 13 with irregular periods thereafter. There was no known exposure to cases of infectious hepatitis or hepatotoxins. Family history was noncontributory.

Admission physical examination revealed a chronically ill, icteric female. Vital signs were normal. Weight was 121 pounds. Spider angiomata were present over the upper thorax and bleeding from the gums was noted. There was evidence of pleural effusion on the right and both diaphragms were elevated. There was a grade II systolic murmur at the apex. The abdomen was distended and a fluid wave with shifting dullness was present. The liver edge was palpable just below the costal margin and was tender. The spleen was enlarged 7-8 cm. below the costal margin. Lower extremities showed 2+ pitting edema extending to knee level. Significant laboratory studies revealed a white blood count of 4000/cu.mm. with a normal differential. Hemoglobin 12 gm. per cent, hematocrit 36 vpc and platelet count of 244,800/cu.mm. Bleeding and clotting times were normal; prothrombin time was 23 seconds with a control of 11 seconds. Serological test for syphilis was nonreactive. Serum bilirubin, 2 mg.

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per cent with 1.0 mg. direct. Thymol turbidity was 12 units, cephalin-cholesterol flocculation 4+, and total serum protein 5.6 gm. per cent with 1.7 gm. per cent albumin and 3.9 gm. per cent globulin. Pleural and ascitic fluid had the appearance of transudate and were negative for bacterial growth and malignant cells. Esophageal varices were noted on gastrointestinal roentgenographic examination. The patient was given routine care with measures to decrease anasarca. Results of the work-up suggested the diagnosis of cirrhosis, probably secondary to hepatitis despite the negative history for such an infection. Portacaval shunt was again considered but felt to be contraindicated.

She was discharged from the hospital to outpatient care, but was readmitted the following day because of vomiting of small amounts of blood. She responded initially to conservative care. Approximately 12 hours later, she developed massive gastrointestinal hemorrhage, and despite replacement with large amounts of whole blood, use of the Sengstaken tube and other supportive measures, the patient died several hours later.

Autopsy findings were compatible with the diagnosis of postnecrotic cirrhosis. Grossly, the liver was small and weighed 750 gm.; there were many nodules of varying size separated by broad bands of fibrous connective tissue. Microscopically, there was evidence of slight parenchymal necrosis, fibrous tissue proliferation with distortion of architecture and bile duct proliferation. The spleen weighed 500 gm. and showed fibrosis and thickening of the splenic pulp. The heart was grossly normal and microscopically only showed slight disorganization of the connective tissue elements of the endocardium below the mitral valve. There were numerous esophageal varices; in one of these a large defect was noted. Bone marrow was normal.

This young female manifested severe changes compatible with postnecrotic cirrhosis. There was no history of infectious hepatitis, the disease was insidious in onset and showed a progressive downhill course.

Comment

Bearn and others[1] have noted that most cases of cirrhosis in young adults which are not due to alcoholism or nutritional deficiency occur in females; this observation has been supported by several other authors[2-4]. Histologically, these cases usually show postnecrotic cirrhosis characterized by areas of necrosis, fibrous proliferation and irregular areas of parenchymal regeneration[3]. In many of the cases, a probable relationship to episodes of infectious hepatitis appears likely[5-7]. This association is further substantiated by the study of Klatskin[8] who reported nine cases of postnecrotic cirrhosis which presumably developed as a sequel to anicteric hepatitis. In this series, eight of the nine patients were female, and biopsies were usually obtained early enough in the course of the disease to show features thought to be diagnostic of hepatitis. All these cases, however, were marked by an acute illness with constitutional symptoms and

definite gastrointestinal complaints. More recently there has been further confirmation of this concept[9], although some authors do not agree[10,11].

On the other hand, there are a number of cases which show no previous history compatible with either typical infectious hepatitis, any acute illness described above which might represent anicteric hepatitis, or exposure to known hepatotoxins. Stuhler[7] did not identify the etiologic agent in 22 of 73 cases of postnecrotic cirrhosis found in a 30-year study of autopsy cases. Bearn[1] was also unable to find any etiologic agent in the majority of his 26 cases. While, however, the symptoms and signs noted in this group were generally similar to those known to develop following infectious hepatitis, there were additional symptoms felt to be unique to this group. These included arthritis or arthralgia in 11, menstrual difficulty in 22, and febrile attacks of an unexplained nature in ten of the patients. Four patients had manifestations suggestive of Cushing's syndrome. Many of these patients appeared well-nourished despite significant liver disease. It was suggested that specific endocrine influences, usually present in young women, might be of importance. Bongiovanni[12] had previously called attention to a group of young women with cirrhosis of undetermined etiology who showed features of hyperadrenalism early in the course of their disease, but he was unable to attach further significance to this finding.

Mackay has reported a group of young women whose disease is described as "lupoid hepatitis"[13]. Twelve of the patients in this group showed the typical histological picture of postnecrotic cirrhosis. In addition, however, all of the group showed a weakly positive *L.E.* cell test; that is, a positive test was found only on a single or infrequent occasions. Also, 11 of 14 patients presented systemic manifestations suggestive of true *lupus erythematosus*. The authors conclude that lupoid hepatitis and *lupus erythematosus* can be distinguished as separate entities with a similar pathogenesis, possibly related to autosensitization. To further contrast the two conditions, they studied 19 cases of typical *lupus erythematosus* and found the liver tissue to be normal or only show minor nonspecific changes. This finding is also confirmed by the studies of Griffith[14] and Harvey[15] who found only slight pathological change, not characteristic of postnecrotic cirrhosis in a large number of cases. Hardin[16] has reported a case of postnecrotic cirrhosis in a 14-year old girl which was mistaken for disseminated *lupus erythematosus* because of widespread, systemic involvement. Repeated *L.E.* preparations were negative and liver biopsy showed the characteristic changes of postnecrotic cirrhosis.

Summary

It appears then that postnecrotic cirrhosis is a fairly common cause of chronic liver disease in young women and that it is probably more common in women than in men in this age group. There is some evidence that the condition is a result of previous infectious hepatitis. Most of the evidence, while

quite suggestive, is indirect, although the findings of Klatskin[8] seem to relate the two conditions more directly. There is still a large percentage of cases where no apparent direct or indirect relationship to hepatitis exists. Some of these cases have an insidious onset, develop the typical picture of cirrhosis, and have no unusual findings. Others show the usual picture but seem to have a hormonal factor, either causally or incidentally, present. Still a third group presents findings which are suggestive of *lupus erythematosus* and show a positive *L.E.* cell test. They also, however, show the pathologic findings of postnecrotic cirrhosis in contrast to classical cases of *lupus erythematosus.*

It may be that all cases have a common etiology, for example infectious hepatitis, with a wide range of expressivity. It may be that there are several, unrelated etiological factors which produce the same pathological picture. If this is true, further understanding of the problem will await the development of more refined diagnostic technics. The problem is nonetheless a serious one which deserves more intensive consideration and investigation.

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THE DECHOLIN TASTE TIME TEST OF LIVER DYSFUNCTION

A Clinical Report on Its Nonspecific Diagnostic Significance and on the Therapeutic Use of Decholin

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The Decholin taste time test is proposed as a convenient and dependable clinical test of liver function which gives a prompt answer, and suggests curative medication.

In 25 years of practice, complaints of gassy indigestion, distress following meals, and constipation have been found due to a liver dysfunction which can be diagnosed as a hepatitis by the Decholin taste time test, and which can be well treated by Decholin medication.

These digestive disorders have been encountered in women, with a completely normal battery of conventional liver function tests, negative gastrointestinal series, normal gallbladder visualization and emptying time, and negative barium enema examinations, who continue to be distressed by indigestion. When "nothing wrong can be found", the woman is not neurotic and a functional indigestion should not be diagnosed. Psychotherapy and tranquilizers will not relieve nor cure intrahepatic cholestasis.

Many women, chronically ill with indigestion and constipation, have a poor Decholin taste time test when no other test is abnormal. This has proved to be a clinically dependable test of liver dysfunction compatible with an insufficient amount of bile secreted into the duodenum. The test is particularly convenient when excellent laboratory facilities are not available, hospitalization is refused, or they cannot well be afforded.

A common cause of gassy indigestion, bloating, "biliousness", and constipation is lack of an adequate amount of bile to completely emulsify ingested fat and so prepare it for absorption by the intestinal villi. A bad, or brassy taste in the mouth, poor appetite, a tendency to obesity—everything turns to fat—full feeling and abdominal distress following meals, excessive belching, borborygmus, and flatus, liver tenderness to palpation, and nervousness are all commonly associated. An adequate amount of bile excretion can be readily estimated by stool color—normally a dark brown color. Light brown to clay-colored stools suggests a deficient excretion of bile. In the absence of surgical disease of the biliary tract, intrahepatic cholestasis describes the liver dysfunction which causes gassy indigestion and constipation.

Indigestion is lack of, or imperfect digestion (Gould). Indigestion in women is often due to inability of the gastrointestinal tract to digest food properly to insure systemic absorption of the nutrients and excretion of waste, par-

ticularly fats. Exceptions are the result of ingesting tainted foods. Wholesome food ingested in sensible amounts does not, in itself, cause indigestion when the gastrointestinal tract is functioning normally. Peptic ulcers are suggested when relief is obtained following meals. Liver and gallbladder dysfunction is suggested when distress follows meals.

The task properly confronting a physician whose patient complains of indigestion is to restore normal digestion. This also entails correct diagnosis of systemic diseases such as hypothyroidism and congestive heart failure, as well as hepatitis and colitis. Low fat diets, antispasmodics, antacids, and tranquilizers may relieve symptoms temporarily but are not curative of pathology.

The Decholin Taste Time Test of Liver Function

Materials:—One 10 c.c. ampule of Decholin Sodium 20 per cent solution (Ames) of sodium dehydrocholate for intravenous injection.

One 10 c.c. sterile syringe with a 21-gauge needle one inch, or more, in length.

Tourniquet—small rubber hose, stethoscope hose is good, and a hemostat for a clamp is convenient.

Wrist watch with sweep second hand.

Technic of test:—Ten c.c. of the Decholin Sodium 20 per cent solution is drawn into the syringe.

It is my custom to have the patient lying comfortably on a couch. An arm vein is used for the injection. There is little, if any, difference in test results whether the right, or left arm vein is used. Clean venipuncture with free flow of blood back into the syringe insures rapid injection with freedom from infiltration which would cause pain and negate the test.

When the arm vein has been entered, the tourniquet is removed and the Decholin Sodium solution is injected intravenously at the beginning rate of 1.0 c.c. every 5 seconds by actual sweep-watch second-hand observation.

Interpretation of the Decholin Taste Time Test

Normal test:—A normal Decholin taste time test is obtained when the patient notes, and reports promptly, the strong, distinctively sour Decholin taste within 15 seconds of the intravenous injection of not more than 3.0 c.c. of the 20 per cent Decholin Sodium solution. Also, when, or if, the strong taste induces nausea, and perhaps vomiting.

When the taste is reported nauseating, the injection is stopped until the taste susides—usually an interval of 10 seconds. Injection is then continued. If

liver function is normal, the strong taste will again be noted promptly with an additional injection of 2.0 or 3.0 c.c. of the solution. It may take 4 or 5 minutes to inject the entire 10 c.c. of solution without causing nausea when excellent liver function exists.

In some instances of abnormal liver function although the taste is noted as strong at 3.0 c.c. at 15 seconds, continued injection of the solution does not cause nausea but instead, the taste fades despite injection of the 10 c.c. of solution within 50 seconds.

As a general statement, the quicker and stronger the taste is noted and maintained, the more normal is liver function.

Abnormal test:—Abnormal liver function is suggested when more than 15 seconds elapse, and more than 3.0 c.c. of the 20 per cent Decholin Sodium solution can be injected intravenously at the rate of 1.0 c.c. every 5.0 seconds, before the distinctively sour taste is reported.

If the entire 10.0 c.c. can be injected within 50 to 60 seconds, with no more than a faint taste at 25 seconds, and perhaps a somewhat stronger taste noted near the completion of the injection, liver function is not normal.

When liver function is abnormal, the taste although noted promptly at 3.0 c.c. at 15 seconds may fade gradually despite continued injection of the entire 10.0 c.c. of solution within 50 seconds.

With few exceptions noted below, a patient whose Decholin taste time test is abnormal will benefit from Decholin medication.

An objection to my interpretation of the Decholin taste time test of liver function states:

"I do not see how a drug administered intravenously, and being measured by the time it produces a taste sensation, could be considered a test of liver function, considering the fact that a portion of the Decholin in the blood stream goes directly to the tongue taste receptors without passing through the liver. The rate of circulation could not be affected by intrahepatic cholestasis and, therefore, disturbed liver function could not be measured by the circulation time procedure"[1].

Admitting that the physiology of the test may not make sense theoretically, in 25 years of clinical experience with the Decholin taste time test as described herein, a "medical" type of hepatitis or cholangitis has been dependably diagnosed which usually responds well to Decholin medication. No other liver function test known has so reliably indicated curative medication. In my experience, intrahepatic cholestasis due to a virus hepatitis can slow the Decholin taste time test, just as can congestive heart failure and cirrhosis of the liver.

Other Liver Function Tests

Electropheogram:—The electropheogram, a protein fractionation of blood serum, reveals liver dysfunctions not suspected by the conventional battery of liver function tests. It is a test which quite accurately suggests a diagnosis of virus (infectious) hepatitis, cirrhosis of the liver, low gammaglobinemia, myeloma, and abnormal albumin/globulin ratios. It has no diagnostic value for intrahepatic cholestasis.

The electropheogram has great value in demonstrating liver dysfunction likely to be confused with intrahepatic cholestasis. Liver tenderness to palpation often persists following apparent recovery from a systemic illness which caused an abnormal electropheogram. A slow Decholin taste time test suggests intrahepatic cholestasis is the sequel of the previous primary hepatitis. Decholin medication frequently benefits those whose abnormal electropheogram suggested a diagnosis of virus hepatitis or an early cirrhosis of the liver.

Purged stool examinations:—to avoid errors of diagnosis and futile medication, it is our practice, when chronic biliary tract dysfunction is present clinically, or demonstrated by the usual battery of liver function tests, to request a purged stool examination for parasites, ova, and pathogenic and normal bacteria[2].

Giardia lamblia:—*Giardia lamblia* infestation of the biliary tract is reported occasionally. It causes severe liver and gallbladder distress which respond well, and promptly, to atabrin medication. *Giardia* infestation of the biliary tract can be diagnosed by a purged stool examination. It is supposed the phospho-soda purge stimulates gallbladder contraction and increased secretion of bile from the liver. The *Giardia* are washed down with the bile and can be identified in the watery stool.

Bacterial hepatitis:—When a purged stool examination is reported positive for a pathogenic bacteria, a bacterial colitis may be present, but the bacteria may also be washed down from the liver and gallbladder. Clinically, a bacterial hepatitis is often relieved by medication indicated by culture and identification of a pathogenic bacteria in a stool specimen, and sensitivity tests against the bacteria identified.

Amebic hepatitis:—When a stool examination is reported positive for the parasite *Endameba histolytica,* a serum cholinesterase test is routinely requested to confirm a clinical diagnosis of amebic hepatitis.

Natural history of human parasitization by E. histolytica:—The sequence of events in the natural history of human parasitization by *E. histolytica* is believed initiated by primary infestation of the fecal matter in the cecum. A positive stool examination indicates only that the parasite is present in the fecal matter, and not that tissue invasion has occurred. For presently unknown rea-

sons, the parasite may become invasive. Only the trophozoite stage is invasive and first invades the mucosa of the cecum but soon spreads to involve the entire colon and rectum. Invasion of the colon mucosa by the trophozoite of *E. histolytica* constitutes a diagnosis of amebic colitis. A diagnosis of amebic colitis should be made only when there is clinical evidence of a colitis and the stool examination is positive for *E. histolytica*. Many people are known to be asymptomatic carriers of the parasite with positive stools but without invasion of the colon mucosa—positive stools without amebic colitis.

Any individual with a stool positive for *E. histolytica* is potentially liable to develop amebic colitis.

Any individual with amebic colitis is potentially liable to develop amebic hepatitis.

The serum cholinesterase test:—When stool infestation by the parasite *E. histolytica* has been reported, the question of extension of the infestation to the liver has always been a diagnostic challenge.

TABLE I

RESULTS OF DECHOLIN TASTE TIME TESTS IN 34 WOMEN WITH A HEPATITIS PERSISTING AFTER APPARENT CURE OF AMEBIC HEPATITIS

Taste time test result	Number of women
Good	3
Fair	12
Poor	19

The serum cholinesterase test uses the acetocholine hydrolyzing enzyme, cholinesterase[3]. When reported greater than 250 units, the test has reliably confirmed a clinical diagnosis of amebic hepatitis in a series of over 225 cases with stool examination positive for cysts, precysts, or trophozoites of *E. histolytica*.

Of 64 women with stool examination positive for *E. histolytica* suspected clinically of having amebic hepatitis, 62 (97 per cent) had a serum cholinesterase test value greater than 250 units. The 2 remaining women had test values of 233 units.

In 34 of these 62 women, after completion of amebacidal medication and negative stool "cure", intrahepatic cholestasis was suspected because of continuing hepatitis—liver tender to palpation with indigestion and constipation. These 34 women were given a Decholin taste time test.

Clinical recovery from the liver soreness to palpation, and the indigestion and constipation, following Decholin medication in these 31 treated women

with fair to poor taste time tests, suggests that intrahepatic cholestasis is a common sequel of amebic hepatitis.

The Decholin taste time test is of no diagnostic value in amebic hepatitis, but it is of great diagnostic value in intrahepatic cholestasis.

Indications for Decholin Medication

The clinical value of the Decholin taste time test is that when fair, or poor, it indicates a type of liver dysfunction seldom diagnosed by other liver function tests. Decholin tablet and intravenous medication is uniformly successful in relieving the liver condition indicated by the poor Decholin taste time test.

Decholin is not an antibiotic. Its therapeutic value is its ability to stimulate liver function in that the ability of the liver to secrete and excrete bile is increased.

Biliary tract indigestion and constipation:—The common, chronic, gassy indigestion and constipation due to poor liver function seen daily by practicing physicians regularly improves following three, or more, daily, or alternate daily, intravenous injections of 10 c.c. Decholin Sodium 20 per cent solution. Tablets Decholin are usually started at a dosage of tablets iii t.i.d., p.c. When a fair to good taste is obtained, there is usually a laxative effect in that the number of daily bowel movements increase to three, or more, daily and become a uniform dark brown in color, and soft, or watery in consistency. Intravenous medication is then stopped and tablets Decholin continued indefinitely.

Nausea, indigestion, and constipation of pregnancy:—Twenty years' clinical experience with Decholin tablets prescribed routinely during pregnancy, in sufficient dosage to insure one or two bowel movements daily, has prevented most of the indigestion, gassy abdominal distress, and constipation commonly annoying during pregnancy.

Edema of pregnancy:—Edema accompanying pregnancy is often benefited by Decholin medication when the Decholin taste time test is poor.

Poor gallbladder function:—Poor gallbladder function, as determined by dye visualization, whether or not calculi are present, is regularly improved by intravenous and oral Decholin medication. Gallbladder visualization repeated 1 or 2 years later is often improved, or normal.

There is also reason to believe that Decholin tablets prescribed routinely during pregnancy, and following delivery when indicated, will prevent calculous cholecystitis in later life. The fair, fat, and forty woman, so frequently the victim of gallstone colic, has usually been the mother of one, or more, children. Significantly, a history of biliary tract type indigestion and constipation of many years' duration, subsequent to her first pregnancy, is regularly obtained and may predispose to calculous formation.

Early cirrhosis of the liver:—Early cirrhosis of the liver regularly gives a slow Decholin taste time test. A great functional burden is placed on the heart by an advanced stage of cirrhosis of the liver. A poor Decholin taste time test clearly measures intrahepatic cholestasis due to an early stage of cirrhosis of the liver before congestive heart failure is present.

Passive congestion of the liver:—Primary heart failure regularly induces passive congestion of the liver and kidneys. Congestive heart failure is indirectly benefited by Decholin medication. The mild, nonirritating, but considerable diuretic action of Decholin has been well established. Passive congestion of the liver is benefited by Decholin medication because the increased bile flow relieves some of the edema.

Jaundice:—Decholin Sodium 20 per cent solution intravenously, and Decholin tablets orally have, in addition to routine medication, helped to clear jaundice promptly, except of course, when there is complete obstruction of the common bile duct, or carcinoma of the head of the pancreas.

Viral hepatitis, infectious hepatitis:—Intrahepatic cholestasis is frequently a sequel of a primary liver infection, such as a viral hepatitis. Convalescence is regularly shortened by exhibition of Decholin medication. In my experience, infectious hepatitis is not a contraindication to Decholin medication.

Decholin Medication

It is recommended that a course of Decholin medication be started with a series of intravenous injections of 10.0 c.c. Decholin Sodium 20 per cent three times weekly. Dosage of Decholin tablets, taken concomitantly with the intravenous injections, is regulated by the number of daily bowel movements. A starting dose of tablets iii t.i.d., p.c., is usually prescribed. This dose is gradually reduced as the number of daily bowel movements exceeds two.

Much more prompt recovery is obtained when medication is started with the combined intravenous and oral medication. Patients who have taken six to nine Decholin tablets daily for a year or more are regularly able to reduce the tablet dosage gradually and stop entirely a few weeks following a series of intravenous Decholin injections.

Diarrhea is the only known side-effect of Decholin overdosage. High dosage is seldom indicated but is occasionally necessary to restore liver function promptly. No undesirable side-effects of large dosage with Decholin Sodium 20 per cent solution intravenously given three times weekly for a total of 29 injections have been noted. Tablets Decholin have been taken orally at a total daily dosage of 32 tablets with no side-effects.

Ingested fat stimulates liver secretion and excretion of bile, and contraction of the gallbladder, just as do bile salts and bile acids. A low fat diet aggravates,

rather than benefits, the already impaired ability of the liver to secrete bile. To restrict dietary fat, other than temporarily, does not make therapeutic sense.

Decholin intravenously and orally has a well established stimulating effect on the liver's ability to secrete bile. Patients with a slow Decholin taste time test treated intensively with intravenous and oral Decholin are soon able to eat fats without distress.

Decholin therapy may unjustly be held accountable for poor clinical results when pathology other than intrahepatic cholestasis is not diagnosed and treated.

Decholin is of great benefit to stimulate secretion and excretion of bile.

Decholin has no antibiotic effect.

A sensation of warmth, with or without cramping, in the arm is infrequently noted during the intravenous injection of the 20 per cent Decholin Sodium solution. This distress subsides within a few minutes and has never been severe enough to induce a patient to refuse another injection. The same vein may be used the following day without a recurrence of the distress. Its cause is not known.

Illustrative Clinical Cases

Three cases of liver dysfunction which responded to Decholin medication are reported. They were selected as unusual, both as to the number of intravenous injections of Decholin Sodium 20 per cent solution administered, and the high dosage of Decholin tablets tolerated without side-effects, and required for cure of the hepatitis.

Case 1:—Mr. T., 62 years. When first seen, Mr. T. was extremely weak physically, obviously ill, and he complained of upper abdominal soreness, abdominal cramps, belching, borborygmus, and flatus, anorexia, "indigestion", and constipation. He had recently been discharged from a large clinic following one month's hospitalization during which many x-ray examinations and laboratory tests had been made (but no stool examinations) without arriving at a diagnosis and with no medication recommended.

His Decholin taste time test was no taste at all with 10 c.c. given in 50 seconds, faint at 8.0 c.c., to slight at 6.0 c.c. given in 30 seconds on successive days. A series of 19 intravenous injections of 10 c.c. Decholin Sodium 20 per cent solution was administered within the next few months. Concomitant dosage of Decholin tablets, at first increased gradually to 24 tablets daily, later gradually reduced to 12 tablets daily, produced only one bowel movement daily. He improved somewhat on Decholin medication, and was fairly comfortable, but abundant vigor was not regained. A flare-up of his complaints occurred shortly after the 19th Decholin injection.

Stool examination at this time was positive for *E. histolytica*. The serum cholinesterase test was 485 units. Diagnosis was amebic colitis and amebic hepatitis.

Systemic and intestinal amebacidal medication was prescribed. Several negative stools were obtained, together with gradual reduction of the serum cholinesterase test values but liver soreness, gassy indigestion, and constipation continued.

The Decholin taste time test was then repeated and again found to be faint at 10.0 c.c. given in 60 seconds. A series of 5 daily injections permitted gradual reduction of the dosage of Decholin tablets from 12 daily until they were discontinued entirely a few weeks later. He since has been free of indigestion and abdominal distress three years and has regained his strength to manage a gasoline filling station.

The electropheogram was normal.

The serum cholinesterase test gradually subsided from a peak of 485 units at the start of the last series of 5 Decholin injections to 275 units one year later. Normal is below 250 units.

The slow Decholin taste time test, and the elevated serum cholinesterase test values, were the only abnormal liver function tests ever reported, yet he was seriously ill and completely disabled when first seen.

This case illustrates the necessity of first overcoming the amebic hepatitis, or any other liver infection or infestation, before maximum benefit will be derived from Decholin medication. Decholin is not an antibiotic. Decholin stimulates liver bile secretion and excretion, stasis of which makes a diagnosis of intrahepatic cholestasis.

Case 2:—Mrs. A., 19 years. This young housewife complained, "I feel wretched". She was also unhappy about two large brownish blotches on her face, resembling the so-called "liver spots" of pregnancy, yet she was not, and had never been pregnant. There was no liver or abdominal tenderness to palpation. "Nothing wrong" had been found on x-ray examinations and laboratory tests taken previously. A daily laxative, or enema, was taken to insure a bowel movement which she stated gave partial relief from abdominal distress and distention. Stool, and rectal examinations were negative.

Mrs. A. took the largest dosage of Decholin tablets daily of any of my patients.

Table II illustrates the dosage of Decholin injections and tablets taken.

Mrs. A. has since been well 3 years without medication. The brownish blotches on her face cleared gradually. One year later her face was free of blemishes. The slow Decholin taste time test was the only abnormality ever

demonstrated. The high range of dosage of Decholin injection, as well as the tablets orally, is unusual in my experience.

Decholin medication apparently cured the cause of the brownish blotches on her face, her indigestion, abdominal distress, and constipation. Intrahepatic cholestasis appears to be an acceptable diagnosis. No undesirable, or any side-effects were noted during the course of medication, or since.

Case 3:—Mrs. R., 53 years. Mrs. R. complained of abdominal soreness, gassy distention, marked borborygmus, flatus, and belching, crampy abdominal

TABLE II

DOSAGE OF DECHOLIN INTRAVENOUSLY AND ORALLY TAKEN BY CASE 2

Date	Number of Decholin injections	Taste time, seconds	Taste intensity	No. tablets Decholin daily
4/25	1	50	no taste	ii. b.i.d.
4/26	2	40	faint at 8 c.c.	iv. b.i.d.
4/30	3	50	no taste	iv. t.i.d.
5/2	4	30	faint at 6 c.c.	14 daily
5/9	5	30	faint at 6 c.c.	14 daily
5/12	6	35	faint at 7 c.c.	22 daily
5/16	7	50	faint at 9 c.c.	22 daily
5/18	8	25	faint at 5 c.c.	28 daily
5/23	9	25	faint at 5 c.c.	32 daily
6/9	10	30	faint at 6 c.c.	28 daily
6/13	11	30	faint at 5 c.c.	22 daily
6/23	12	20	faint at 4 c.c.	14 daily
6/27	none	—	—	3 t.i.d.
7/13	none	—	—	stopped tablets

pains, indigestion, cramps, and bloating following ingestion of sweets, a craving for pickles and sour foods, and chronic asthenia among a host of complaints of many years' duration.

In May and June of 1957, she was successfully treated for amebic colitis and amebic hepatitis—stool tests have since remained negative and normal serum cholinesterase tests have been reported.

The liver, and much of the colon and small intestinal tenderness to palpation continued although most of the crampy pains and gassy distention sub-

sided. Because of a very poor Decholin taste time test, a series of 29 intravenous injections of 10 c.c. Decholin Sodium 20 per cent solution was given from 5 July to 8 September 1957 with not a single good taste time noted. Eight Decholin tablets were prescribed daily which insured one bowel movement. Some additional relief from indigestion was reported, but a great deal of liver and intestinal tenderness to palpation persisted.

On 21 October *Salmonella enteritidis* was cultured from her stool. An extremely low normal, fecal, bacterial count, and abundant overgrowth of yeast-like organisms resembling monila were also reported.

Culture and sensitivity tests of the *S. enteritidis* indicated Chloromycetin which successfully eradicated the pathogen from the stool.

Mycostatin destroyed the monila.

Typhoid vaccine was given to increase resistance to reinfection with Salmonella organisms.

A bacterial culture closely resembling the normal, fecal, bacterial flora, Lacto-Bac (Dowell Laboratories, Mesa, Ariz.) was prescribed as a yogurt-like milk drink to implant a normal, fecal, bacterial flora.

In addition to the bacteria implanted, Malt Soup Extract (Borcherdt) powder acts as a culture media and stimulates growth of the normal bacterial flora, and was prescribed with the Lacto-Bac. The Malt Soup Extract powder is also prescribed alone to increase low fecal bacterial counts.

Decholin tablets were continued iv a.m. and iv p.m. Liver tenderness to palpation improved somewhat but did not abate entirely.

On 17 January 1958 stool culture grew out *Shigella ceylonensis*. Sensitivity tests indicated Tab. Furoxone which was prescribed. Two stool check-up examinations were entirely negative, yet some liver tenderness and gassy indigestion continued. The serum cholinesterase test and electropheogram were both normal at this time.

From 4 March to 31 March 1958, 15 intravenous Decholin injections were given. The Decholin taste time improved steadily, liver tenderness, and gassy abdominal distress gradually subsided. A gradual reduction in dosage of Decholin tablets was possible. Appetite improved and neither fats or sweets now caused distress. Asthenia is the last complaint persisting but is declining.

This case illustrates a physician's utter dependence upon competent stool examinations for correct diagnosis and medication of intestinal tract disorders. No previous medication had ever given relief. Hysterectomy had not relieved the pelvic distress which was secondary to the colitis. A low normal, intestinal, bacterial flora regularly causes indigestion and colon tenderness to palpation, as does overgrowth of yeast. Decholin therapy was not successful until the

bacterial and yeast infections, as well as the amebic infestation, were overcome. The residual intrahepatic cholestasis, which is a sequel of many systemic illnesses, cleared promptly with intensive Decholin medication.

Summary

A slow intravenous Decholin taste time test signifies a type of liver dysfunction causing a decrease in the amount of bile secreted within the liver and excreted into the duodenum. The term intrahepatic cholestasis accurately describes the pathology believed present when the Decholin taste time test is poor. Intrahepatic cholestasis may, however, be a residual hepatitis the sequel of a specific bacterial, virus, or amebic infection which demands specific medication.

The Decholin taste time test, when performed as described, is safe. The only contraindication is mechanical obstruction of the common bile duct.

Intravenous Decholin Sodium 20 per cent solution and tablets Decholin orally are excellent stimulants to liver secretion and excretion of bile. Twenty-five years personal use has proved them dependably effective when indicated by a poor Decholin taste time test. They are also beneficial in treatment of jaundice not due to complete obstruction of the common bile duct, virus hepatitis, early cirrhosis of the liver, passive congestion of the liver accompanying congestive heart failure, and the indigestion and constipation common during pregnancy.

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SAINT'S TRIAD; CHOLELITHIASIS, HIATUS HERNIA, AND DIVERTICULOSIS OF THE COLON IN THE SAME PATIENT

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Early recognition of all lesions is important in evaluating the exact clinical status of a patient and thus will help in obtaining a more satisfactory response to treatment. A frequent site for the location of multiple abnormalities has been the gastrointestinal tract where the dual combinations of hiatus hernia with either cholelithiasis or diverticulosis of the colon have often been encountered[1-4]. At times the coexistence of these double lesions will cause some delay in reaching an exact diagnosis; when more than two occur in the same patient then the difficulties may be enhanced greatly.

The grouping of the three conditions of hiatus hernia, cholelithiasis and diverticulosis of the colon in an individual is, therefore, of even more interest. The demonstration of all these lesions in a patient was named Saint's Triad by Muller[5] in 1948, and since then this association has been noted frequently. He emphasized the importance of a complete x-ray investigation to discover all alterations in the gastrointestinal tract since there may be considerable overlapping of the symptoms produced by each member of the triad. This thorough survey will help in reaching a decision for the proper choice of therapy and so may tend to reduce the occasional unsatisfactory results obtained in treating digestive complaints. Unless the exact status of the gastrointestinal tract is clarified, treatment, medical or surgical is sometimes misdirected at a condition first diagnosed but which actually may be asymptomatic or contribute least to the patient's discomfort, while the more distressing lesion may be completely overlooked. This may be illustrated by the occasional persistence of symptoms in a patient, following cholecystectomy, which ultimately may be shown to be related to a previously unappreciated hiatus hernia rather than to the gallstones recognized first. The resemblance in the symptomatology of hiatus hernia or cholelithiasis to that of coronary artery disease may add to the diagnostic difficulty, since Saint's Triad is found more often in the older age groups where this type of heart disease is most common.

The etiology of Saint's Triad is not known nor has it been established whether these associated lesions are the result of a single pathogenic cause which is responsible for their development, or whether they appear as the consequence of multiple factors acting independently. Some of these points are illustrated in the following case.

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Case Report

Patient G. B., age 69, white female was admitted to the hospital for the second time on 22 August 1958, because of a burning pain over the precordium radiating to the left shoulder and left arm for two hours, together with nausea, vomiting and dizziness. She had been treated previously at the hospital for a myocardial infarction and discharged in good condition in June, 1958.

Past history revealed that about 40 years ago, cholecystostomy was performed and a "bag full of stones" removed. Patient felt well for about a year following the operation, when she again noted the onset of gastrointestinal complaints which constantly have recurred up to the present admission. These consisted of heartburn shortly after eating, occurring most frequently at night in the recumbent position; relief was usually obtained by sitting up, and the ingestion of bicarbonate of soda or vomiting. Bowels have generally been normal, the patient requiring an occasional dose of milk of magnesia; obesity has never been present. Patient had two pregnancies and a hysterectomy was performed 20 years ago.

On physical examination the patient was conscious, alert and not in acute distress. No cyanosis or dyspnea was present. The pupils were equal, reacted to light and accommodation. Heart sounds were of good quality with regular sinus rhythm and no murmur was heard; blood pressure was 100/65. The lungs were clear. The abdomen was soft, not tender and the liver and spleen were not palpable. There was a well healed scar of a past operation in the right upper quadrant. The extremities showed two plus edema and the reflexes were physiological.

The admission blood count revealed a hemoglobin of 12.5 gm., and a white cell count of 12,000 with 85 per cent polymorphonuclear cells, 14 per cent lymphocytes and 1 per cent monocytes. The urine was normal. The fasting blood sugar was 80 mg. per cent and the blood urea nitrogen was 15 mg. per cent. The sedimentation rate was 24 mm. in one hour, and Mazzini was negative. The transaminase test showed the presence of 135 units. The electrocardiogram indicated changes compatible with a posterolateral infarction of the myocardium. Treatment was begun with bed rest and the use of anticoagulants. The original chest complaints soon abated and the patient became comfortable except for the persistence of the digestive symptoms of heartburn, epigastric distress and fullness in the chest; some relief was obtained with antacids. About six weeks after admission, x-ray studies were instituted.

A gastrointestinal series revealed the presence of a large hiatus hernia and diverticula of the duodenum. No ulcer was noted. Since the original operation consisted only of removal of the gallstones with retention of the gallbladder it was deemed worthwhile investigating its function by x-ray. After administra-

tion of the dye, no calculi were noted in the gallbladder which appeared essentially normal except for diminished concentration of opaque material.

Palmer has pointed out that if a patient with a hiatus hernia has either cholelithiasis or diverticulosis of the colon, the probability of the other condition being present is greatly increased[6]. A barium enema, therefore, was obtained although the patient had no symptoms suggestive of disease of the large bowel. This revealed many diverticula along the entire course of the colon, and thus were demonstrated the three components of Saint's Triad—hiatus hernia, diverticulosis of the colon and gallstones which had been removed 40 years ago.

The patient was then treated with antacid, small feedings and placed in the upright position after meals. Most of the symptoms which had been attributed to coronary artery disease were alleviated and the patient was discharged in good condition.

Comment

The combination of cholelithiasis, hiatus hernia and diverticulosis of the colon has been recognized in a significant number of individuals. Following Muller's original description in 1948, Palmer reported five cases of Saint's Triad in 1951 and later was able to collect a larger number obtained from further surveying a series of patients with known hiatus hernia[6,7].

Foster and Knutson[8] reviewed the records in a diagnostic clinic of 713 individuals who had a complete x-ray investigation with a gastrointestinal series, barium enema and gallbladder series and noted that 3.4 per cent had all three components of Saint's Triad. The authors consider this figure significant since they believe their data indicates that the incidence of the triad in this series was eight times higher than would be anticipated by chance alone. Some objection has been raised to this conclusion and it has been suggested that the occurrence of the triple lesion in one patient is only a coincidence. The report, however, still serves to point out the frequent appearance and clinical importance of multiple conditions in the gastrointestinal tract.

The etiology and pathogenesis of Saint's Triad has not been elucidated. Although it is conceivable that two of the manifestations might be the result of a common cause, no single satisfactory mechanism has been proposed which would adequately explain the appearance of all three lesions. Hiatus hernia and diverticulosis of the colon might be jointly produced by changes in pressure both within the abdominal cavity and within the lumen of the colon, or weakness of congenital origin in the diaphragm and in the wall of the colon might underly the appearance of the two pathological states in these areas. The relation of cholelithiasis with the other two manifestations, however, is not clear, so that as Palmer observes, it is difficult to incriminate a single agent which individually could produce all three lesions. Because of this considera-

tion, it has been suggested that Saint's Triad is a syndrome resulting from the varying interplay on the abdominal cavity of multiple factors such as constipation, advancing age, obesity, multiparity and congenital weakness. The findings in the patient presented seems to be compatible with the concept that more than one cause is significant in the evolution of Saint's Triad. It is of some interest that there is seen no recurrence of the gallstones, 40 years after the operation for their removal. It appears that the factors which originally caused the formation of the calculi were no longer in effect. The appearance of diverticulosis and hiatus hernia in the patient with no recurrence of cholelithiasis, even though the gallbladder is still present, seems to suggest that different agents, acting independently on each manifestation, are instrumental in the cause of Saint's Triad. Rather than being produced by a common cause, each component of Saint's Triad is probably a response to its own specific stimuli.

Summary

The presence of the multiple condition of cholelithiasis, diverticulosis of the colon and hiatus hernia (Saint's Triad) occurring in a patient may cause some diagnostic difficulties particularly if associated with coronary artery disease. The pathogenesis of this triad is not known but the three abnormalities probably are brought on by combinations of diverse factors such as multiparity, obesity, constipation, age and congenital weakness rather than being caused by a single etiological mechanism. A case of Saint's Triad is presented which illustrates some of these points.

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SYMPOSIUM ON APPENDICITIS

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Appendicitis is today one of the commonest diseases of the abdomen that calls for surgery. It is considered in the United States to be one of the chief causes of death in patients between 15 and 25 years of age. If we take into account the subclinical light attacks that some suffer, it will not be an exaggeration to affirm that half of the population of the world suffers from it during life time (Pedro-Pons).

The appendix, called by some (because of its action in catching up the invading germs) the "abdominal tonsil", is the sentinel of the second gate of the alimentary canal; the sentinel of the first gate being the tonsils. Practically speaking it is a useless inheritance or rather a nuisance. It is prone to inflammation because of its narrow lumen (1 to 2 cm.), thinness of its walls rendering it more vulnerable and less resistant. Many a wandering germ and parasite find their refuge and ease in its hospitable safe harbor.

Appendicitis was definitely added to the long list of abdominal pathology in the last decade of the past century, when a classical communication appeared in 1886 by R. H. Fitz. This was followed by that of McBurney who in 1889 had already performed eight appendectomies on acute cases and devised his special surgical technic used even to this day. The appendix was destined to tag McBurney's name to posterity through his famous point. Full credit, however, is to be given to Heister who was first to describe it anatomically after death in 1755 and to Mestivier who recognized it before death in 1759. Melier was first to publish a study about it and advise surgical intervention as a remedy in 1827. Dupuytran headed the opposition arguing that an insignificant organ like the appendix cannot cause acute symptoms of importance. Fitz coined the term appendicitis.

American surgeons were indeed pioneers in the recognition and study of the disease. Special mention should be made of J. B. Murphy whose five cardinal clinical symptoms of acute appendicitis are classical, and T. G. Morton who in 1887 performed the first successful appendectomy of an acute case, followed by European masters: Treves in England who in 1888 did the first appendectomy of chronic appendicitis (recurrent attack); Dieulafoy in France, Mickulicz in Germany, Roux in Switzerland and Urrutia in Spain.

Frequency of appendicitis is due to frequent intestinal infections (amebiasis, shigellosis, salmonellosis, especially typhoid and paratyphoid). Its frequent diagnosis is due to the better means at our disposal, such as, skiagraphy and other laboratory aids which, when considered jointly, enable us to establish an

accurate early diagnosis and thus save a victim at the appropriate time. For this reason no more frequent cases of rupture or peritonitis are seen. It is a disease that respects no age; however, it is more the property of youth and young adults, rare in children below three and in the aged above 50. In the latter, generally, the appendiceal tissues atrophy with the wear and tear of years and turn into a hard closed excluded tube. It is more common in males (4:1) and often runs in families: 40 cases have been reported in one family. As to size, it may be rudimentary, attaining maximum length of 30 cm., or congenitally absent, split by a septum or even in rare instances it may be double. The first case of double appendix in the annals of medical literature in Mexico was a lucky accidental finding presented by the author before the National Academy of Medicine in 1931. As to shape, it may assume different forms: coiled, bent, folded, dolicho or mega-appendix. As to location, it wanders and may be found anywhere in the abdominal cavity: 1. ascending laterocecal–external or internal–, retrocecal–common–, subcecal, retroileal and anteileal–rare–, retrocolic, extending to transverse colon, kidney, liver, gallbladder; 2. descending extending to true pelvis (pelvic–often 20 per cent), ovary, tube, bladder, rectum, hernial sacs (inguinal or femoral); 3. left-sided (long appendix bridging over true pelvis and adherent to sigmoid) (Fig. 1) or transposed with cecum and right colon to left fossa.

Infection is beyond doubt chief cause of appendicitis either by direct invasion of: 1. local bacteria residing in the lumen when they become virulent and when local defense of the appendicular wall is diminished by allergic reaction or any other cause chiefly obstruction; or of 2. different germs from the intestines or through blood stream. Stasis due to obstruction is an essential factor in the formation of the process. Obstruction may be partial or total, momentary or definite; may arise from new visitors, e.g. intestinal parasites, gallstones, appendicoliths or distention by gas, membranes, bands, adhesions or sustained disposition. As to parasites there is no definite accepted evidence as yet of their direct role, their action is probably mechanical. The usually accused parasites are: *Ascaris lumbricoides, Tenia saginata, Enterobius vermicularis, Trichuris trichura* and *Schistosoma mansoni.* Gallstones and appendicoliths have a similar role. Sometimes, however, appendicular obstruction may exist without any ensuing inflammation. A focal infection in the tonsils, teeth or mesenteric glands is incriminated as well and particularly so are flare-ups. Among predisposing factors mention should be made of grippe, lymphangitis (tonsilitis, mesenteric adenitis), acute fevers, physical fatigue, change of food. Severe trauma to right lower abdomen may cause acute appendicitis.

The habit of squatting in defecation helps in the expulsion of the contents of the appendix and thus participates perhaps in preventing obstruction. This may contribute to the infrequency of the disease among peoples who are not yet familiar with the use of modern means of present civilization.

Pain in acute appendicitis as in any other case of acute abdomen, is the chief symptom. Its onset is sudden and differs in intensity—mild tolerable, or severe colicky, with exacerbation. Pain immobilizes the patient who tries to keep the same position in bed with knees drawn up. Although subjective pain may remit for a while, pain on palpation is always present.

In typical cases pain appears suddenly with great intensity referred either to the epigastric, umbilical or pelvic region to localize itself a few hours later—3 to 36—over the cecoappendicular area in the right iliac fossa. Pain is continuous with exacerbation. In atypical cases, pain may be at the level of the iliac crest behind (retrocecal appendicitis) or in the medial region in what French authors call mesoceliac appendicitis; down in the pelvis, suprapubic referred to bladder and testes accompanied with painful micturition; or left-sided as in transposition of viscera or in the case of long appendix adherent to the left iliac fossa. Acute diverticulitis of the distal portion of the left colon and sigmoid, which is not rare, may give the classical symptoms of an acute appendicitis, hence the term, "left-sided appendicitis".

Mild initial symptoms, chiefly pain, or when alarming symptoms and brutal pain subside suddenly, are both deceiving and of bad omen; they may herald beginning of gangrene or peritonitis. In toxic appendicitis insignificant pain accompanied by severe general symptoms, especially abundant vomiting, is of grave prognosis. Beware and be on the lookout for a "soft belly peritonitis" where apparently symptoms disappear to cover a gangrenous process.

Vomiting is early, comes a few hours after onset; it is very frequent in children and usually opens the scene, being sometimes the only symptom. Some cases are ushered in by abdominal rigidity *d'emblé*, others may take a treacherous clinical course starting with simple manifestations to develop into serious sequela.

In a suspected case of acute appendicitis the duty of the family is to put the patient to rest in bed, give him nothing by mouth and avoid laxatives, purgatives or enemas until the physician's arrival. Purgatives and enemas may cause peritonitis. The duty of the physician is to avoid external applications: ice-bag or hot water bag unless the patient is really relieved by either; to avoid narcotics (morphine, paregoric, or demerol) which might mask symptoms and mislead the diagnosis, unless pain is intolerable. Antispasmodics (atropine, etc.) do not relieve appendicular pain.

Acute Appendicitis in Children

This is preceded by chills, convulsions and vomiting with rise of temperature followed by diarrhea and bloatedness. Pain rarely localizes itself. The child may complain of a wave of general pain in the abdomen that lasts a few

moments and ends in vomiting. Vomiting as we have mentioned above is sometimes the only symptom that opens the scene. In rare cases acute loss of appetite suggests possible appendicitis.

I remember the case of a girl of four who suddenly had a spell of vomiting and slight rise of temperature that lasted a few hours. I suspected acute appendicitis and called in a surgeon. We, as usual, did not agree on the diagnosis and ordered a blood count which proved to be within normal limits. Next day the child was up and feeling fine. Five days later another similar attack occurred and we decided to intervene. We found a congested angry looking appendix.

Acute Appendicitis in the Elderly

Acute appendicitis in the elderly is more frequent than expected. It deceives the clinician because as tissues are worn, reaction is feeble. The clinical picture differs as well. Acute symptoms begin gradually with vague antecedents. Pain is not the first symptom, not well defined or localized; alteration of pulse and temperature is rare; if temperature does exist it is not so high, and may even remain normal. Vomiting is not frequent. Chills on the contrary are frequent and of bad omen; expected muscular rigidity not existing; leucocytosis not so marked —all of this is due to low defensive power in old age. Palpation provokes no pain, and bloatedness and tenderness of abdomen are insignificant. Diagnosis in such cases is in reality very difficult. On the whole the disease is serious because of the condition of the vascular system and of the rapid and early complications: gangrene (massive), abscess formation (not walled-off easily) and perforation. Mortality is high.

Acute appendicitis has the characteristic tendency to abate, cease and then recur with more or less molesting symptoms during intervals of these stages. Even some of the acute cases are nothing but acute manifestation of an asymptomatic silent chronic appendicitis—the so-called chronic appendicitis *d'emblé* that has never before given rise to trouble. The chronicity is proved by the anatomopathologic changes discovered at operation and by histologic examination.

Nonacute or Chronic Appendicitis

There is a great controversy among members of the profession concerning chronic appendicitis. Whilst some believe chronic appendicitis to be a morbid entity, others do not. Some of them go to the extreme of even denying its existence. Experience teaches us to always be prudent and never dogmatic. We share the firm belief that chronic appendicitis is a sobering truism. Its diagnosis should be, however, thorough, exhaustive and meticulous. There is no dogmatic clinician who has not had more than one sad experience because of his obsti-

nate refusal to admit the diagnosis of chronic appendicitis, and the failure no doubt curbs his conscience in his leisure hours and private reflection.

Great stress should be put on the past history of the case, on the recurrent attacks, slight or molesting pain, spontaneous or provoked, momentary or persistent, diffuse or localized. The so-called chronic appendicitis is the sum total of successive mild acute or subacute attacks.

Symptoms that lead to suspicion of chronic appendicitis are: indigestion, anorexia, loss of weight and pain in the right iliac fossa. The patient describes

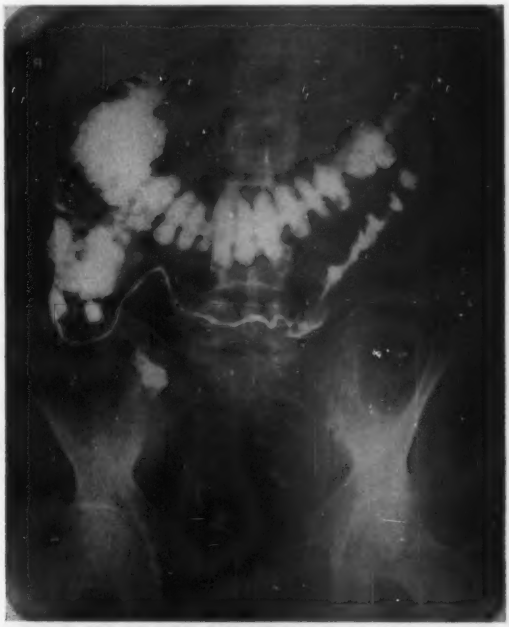

Fig. 1—Long appendix bridging over true pelvis and adherent to sigmoid. (Courtesy of Dr. Saleeby, Radiology Department, American University, Beirut.)

pain as inconstant, coming after physical strenuous exertion or heavy meals, jumping or even after coition or constipation. He says pain at times resembles pressure of a heavy weight referred by some to the epigastrium, by others along the right leg or even simulating right sciatica (Gutmann). Pain may appear at intervals of days, weeks or even months which probably indicates a flare-up of the inflammation. Pain may come in spells lasting a few moments due to dilatation of the lumen by gas. Pain is provoked sometimes by rectal or vaginal examination. Absence of pain may shake the faith of both patient and physician and especially the radiologist.

In a series of 500 of our cases, seen in the course of ten years, who presented the above-mentioned symptoms, 80 per cent revealed anatomopathologic changes and 50 per cent parasitosis.

Diagnosis of chronic appendicitis is not as easy as one might think. A review of the whole abdominal pathology is necessary in order to warrant mistakes.

Hematologic findings:—In so much as the blood picture in acute appendicitis is on the whole indicative and reliable, in chronic cases it is not so sig-

Fig. 2—Residual barium in appendix 72 hours after cecum evacuation. (Nimeh, W. and Reina, B.)

nificant. In acute toxi-infectious cases leukopenia may exist. In both acute and chronic, hemogram may be within normal limitation especially in the early stage of the former. Mononucleosis has been considered as a frequent sign of the chronic process.

Roentgenologic findings:—In so much as skiagraphy in chronic appendicitis is indicative and reliable, in acute appendicitis it is unreliable, not indicative and even dangerous before the acute stage subsides entirely. A scout film of the

abdomen, however, may disclose presence of gas in cecoappendicular region indicating a perforation of the appendix or elsewhere in the abdomen in case of perforation of another viscus especially duodenal ulcer.

Roentgenology is basic in the diagnosis of chronic appendicitis. Pain localized over a visible appendix (appendix visualized in 25 per cent of cases), or in the appendicular region is indicative of an inflammatory process. If it does not exist, elimination of the disease is not by any means conclusive.

The author together with Reina and S. Gonzalez de la Vega have been for years practicing a test that seems to them very satisfactory. While screening the abdominal cavity and having the finger over the tender or painful spot in the cecoappendicular region you are exploring, ask the patient to cough. Cough will displace the abdominal organs. If the visualized tender or painful appendix does not change its place, it is fixed and pathologic. If the spot follows the displaced appendix, it is likewise an indication of an inflammatory condition with no adhesions. If the painful spot does not follow the displaced visible appendix, but remains where it is, the test is negative; it is not appendicitis. If the appendix is invisible and pain does not shift, the test is very probable. If the appendix is invisible, the test is not definite that appendix *per se* is pathologic.

Indirect symptoms are stasis (gastric, duodenal, cecal) and spasm of the esophagus, stomach, duodenum, colon.

Essential findings besides pain are the anatomopathologic changes, such as: 1. fixation of the appendix to any of the adjacent organs (cecum, ileum, ureter, ovary, uterus, sigmoid, rectum, jejunum, liver, gallbladder, transverse colon, psoas, etc.); 2. malformation of the appendix, a) organic due to adhesions, strictures, bands, kinks, membranes, stercoliths, parasites, atrophy; or b) functional due to irritation and spasm giving appendix beaded, segmented or filiform tubular shape; 3. malformation of the inferior pole of the cecum or ileocecal region due to adhesions or spasms projecting bizarre diversity of shadows; 4. residual barium seen in the appendix after the cecum has already evacuated its contents. Residue may be visible days and days later (Fig. 2).

Histologic findings are decisive in confirming diagnosis of chronic inflammation (chronic inflammation, sclerosis, atrophy).

Chronic appendicitis in children is very frequent; in old age very rare. Between 5 and 15, a typical case presents: megalic liver, false diarrhea, pain on palpation in right iliac fossa with general signs especially anemia and anorexia.

In pregnancy clinical symptoms are vague. Pain is localized in the upper part of the right flank; sometimes it may provoke incoercible vomiting and abortion. Chronic appendictis is incriminated in exposing about 10 per cent of females to sterility due to adhesions.

A multipara of three months' pregnancy was caught suddenly by severe abdominal pain, chills and fever. Vaginal bleeding followed in a few hours, heralding, probably, a threatened abortion. Hyperleucocytosis, traces of albumin in the urine and abundant biliary pigments; antecedents; intestinal amebiasis. In a few hours pain localized itself high in the right hypochondrium, intermittent with exacerbation (a differential sign against abortion) with slight muscular defense on palpation. Laparotomy disclosed an inflamed long appendix adherent to the fundus of the uterus. The mucopurulent contents of the appendix—cultured coli bacilli in abundance. Patient recovered without incident and gave birth at term to a fine baby boy.

Hysterical appendicitis in psychoneurotics is not infrequent. It is an appendicophobia that should not be overlooked.

Chronic appendicitis may eventuate in the long run in a mucocele or pseudomyxoma.

Cancer of the appendix is very rare; it occurs between the age of 20 and 30 mostly in women, It develops on the tip of the appendix where a hard body is felt. It does not metastasize.

Treatment

Treatment is: 1. prophylactic to avoid recurrence of acute attacks and to avoid complications; 2. curative, rarely. Symptoms persist more or less in the majority of cases.

Treatment of appendicitis, acute or chronic, is according to unanimous opinion, surgical. The saying, *"Il n'y a pas un traitment médical pour l'appendicite"*, "There is no medical treatment for appendicitis", is the golden rule.

When signs of intestinal infections are present, they should be first treated with antibiotics (aureomycin, streptomycin, tetracycline) and insoluble sulfas (suxadine, guanidine, thaladine) before intervention (A. Ayala Gonzalez).

When should a case of appendicitis be operated upon? As soon as a correct diagnosis is established—without hesitation or postponement. This radical measure has saved the life of many a patient and thanks to it less complications are met with, so much so, that we rarely operate anymore on perforated or abscessed appendices. Why the operation? To avoid recurrence of attacks and to avoid complications; rupture, peritonitis, abscess formation and perivisceritis. This last is one of the reasons why operated patients do not obtain definite results. Do not temporize. It is safer as Gosset stressed, to open an abdomen, to deliver a sane appendix than to leave it there with doubt. In timely diagnosis mortality is less than 1 per cent.

It is discouraging indeed to find that some physicians advise, or rather encourage, the patient and family to postpone surgical intervention, or to give

it up completely. Acute or subacute inflammation may subside and attacks become chronic or even leave the patient in peace for years, or a chronic process may flare up any moment and become acute. But this will not warrant recurrences and sequela at any time. The patient lives, so to speak, with the sword of Damocles over his tummy!!

Antibiotics and/or sulfamides should be administered before and after operation.

The "button-hole" incision which made some surgeons famous especially among the fair sex, should be abandoned except in certain cases particularly in whom no pathologic appendix is found and the operation is *"de complaisance"*. A large incision allows the surgeon to work more freely and explore thoroughly. Moreover, a large incision will enable the surgeon to explore the ileum which must be done at least to a distance of 50 cm. from the ileocecal insertion in search of a possible Meckel's diverticulum.

Pitfalls in Diagnosis

All diseases that constitute an acute abdomen should be differentiated before an acute appendicitis is established.

Acute appendicitis may simulate perforated duodenal ulcer; perforated gallbladder; acute salpingitis; acute ileitis; acute cholecystitis; pneumonia with abdominal stitch; Meckel's diverticulum; hematocele; acute diarrhea; acute pancreatitis; intestinal obstruction; tubal pregnancy; nephrolithiasis; strangulated hernia.

Masked acute appendicitis is not rare especially when the appendix is retrocecal. In these cases pain is referred either to the epigastric region, it is intense lasting a few days only without any digestive antecedents; or to right hypochondrium, pain shooting to shoulder and along right arm without any vesicular antecedents. In both eventualities no physical sign whatsoever is elicited in the cecoappendicular region.

Chronic appendicitis may simulate chronic cholecystitis; chronic salpingitis; ureteral stone; subclinical abscess of abdominal wall; old tuberculous glands; idiopathic right hydronephrosis; parietal abdominal neuralgia; when duodenal ulcer pain is unusually referred to the right iliac fossa; congenital membranes; actinomycosis; hypersensitivity of abdominal distribution of the 12th thoracic and 1st lumbar nerves in the right side (Bockus); ileocecal tuberculosis; mobile cecum.

Differentiation is difficult in lymphadenitis of mesenteric glands; ruptured Graafian follicle in young women; torsion of small ovarian cyst; ruptured diverticulum of ascending colon; acute salpingitis; inflamed Meckel's diverticulum; perforation of cecum; acute ileitis.

It is not uncommon to find, simultaneously in the same patient, at the same time, two or three localized painful spots: appendicular and vesicular, appendicular and epigastric, or appendicular, epigastric and vesicular. Also it is not surprising when skiagraphy alone, or with surgery, confirms the concomitant presence of appendicitis with cholecystitis, simple or calculous, and/or duodenal ulcer.

Coexistence of appendicitis with cholecystitis, simple or calculous, appendiculovesicular syndrome, was first pointed out in 1906 by Dieulafoy. Enriquez in 1910 was a pioneer in calling attention to the possible association of appendicitis with gastroduodenitis or ulceration. The etiopathology of this affiliation is attributed to appendicular procedence.

We were called in consultation for a thin jaundiced patient with low fever and palpable painful tumefaction in the right iliac fossa which we presumed to be either an appendicular abscess or a tuberculoma of the cecum. Laparotomy disclosed, to our surprise and deception, a ptosed inflamed calculous gallbladder.

A suffering young girl who exhausted many physicians for an abdominal pain never localized nor regular nor periodical, causing anorexia, anxiety and emaciation without medical or roentgenologic indicative findings, proved on laparotomy to be a right cystic ovary. Intervention was sufficient to relieve her complaints.

Another patient suffered chronic easy pain in the right iliac fossa accentuated on standing. Tentative diagnosis was chronic appendicitis which was refuted on roentgenologic exploration and blood count. A urography ordered to complete the general check-up revealed a kink in the right ureter at the level of the iliac crest corresponding to the cecoappendicular region. The pain disappeared nearly always on lying down.

An adult of 40, thin, nervous and active complained of distress in his right loin, continuous especially on exertion shooting down the right thigh. At times he felt feverish and giddy. Blood picture normal; x-ray, negative. On palpation a tender mass somewhat superficial and slightly movable was felt in the right lower quadrant suggesting the possibility of chronic appendictis. Intervention discovered a subclinical abscess in the abdominal wall.

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EFFECTIVE NONSPECIFIC TREATMENT OF DIARRHEA

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The problem of providing symptomatic relief for the patient suffering from chronic diarrhea is often a frustrating one. Fortunate, indeed, is the occasional patient (and his physician) whose diarrhea stems from a disorder for which specific therapy is available. Much less fortunate is the usual patient who suffers from an etiologically obscure type of chronic diarrhea. It is not surprising, therefore, that the latter patient with his distressing problem is inherited eventually by the gastroenterologist.

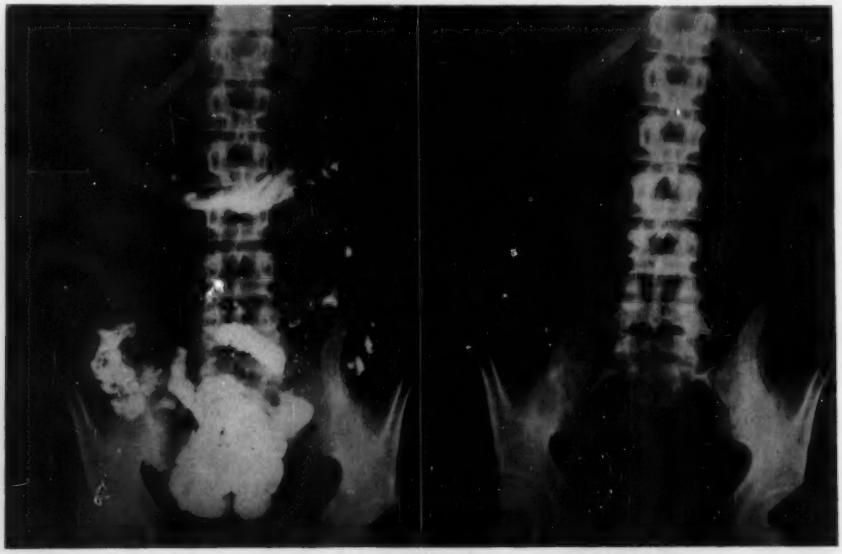

Fig. 1a

Fig. 1b

Fig. 1a—Three-hour control film shows stomach almost completely empty with most of the barium in the terminal ileum.

Fig. 1b—Twenty-four-hour control film shows colon empty.

The multiplicity and variety of drugs used for the symptomatic treatment of diarrhea, ranging from potent opiates to inert clays, reflect the unavailability of an ideal or even a superior antidiarrheal agent. While the opiates have an almost uniquely reliable antiperistaltic action, the risk of addiction limits their use for controlling diarrhea to short-term administration. Further, the spasmogenic and central depressant actions of the opiates may occasionally lead to undesirable pharmacologic effects. Numerous anticholinergics also are em-

ployed, with varying degrees of success, to decrease the intestinal hypermotility associated with diarrheal states. Administered in adequate dosage, the anticholinergics inhibit hypermotility of the bowel but also frequently cause unwanted parasympatholytic effects. Similarly, the use of intestinal adsorbents and demulcents such as kaolin and pectin has not been too rewarding.

The diarrheal state, irrespective of its cause, is characterized by excessive fluidity of stools and hypermotility of the bowel. Sorboquel®, a new composition that acts to reduce both stool fluidity and bowel hypermotility, would thus seem to provide a rational approach to the problem of nonspecific antidiarrheal

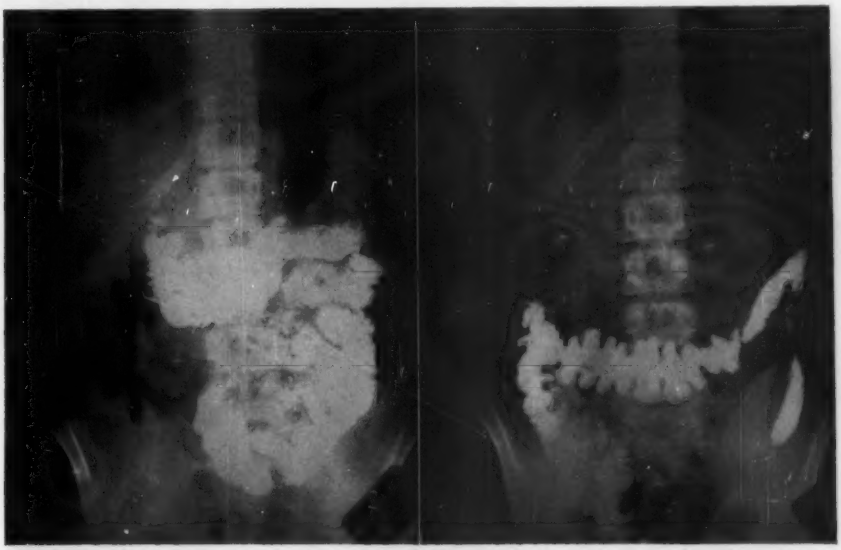

Fig. 1c Fig. 1d

Fig. 1c—Three-hour post-treatment film shows stomach to be partially empty with most of the barium in the jejunum.

Fig. 1d—Twenty-four-hour post-treatment film shows barium outlining the entire colon. Fluoroscopy at 48 hours also revealed barium outlining the colon.

therapy. This preparation is a tableted combination of *polycarbophil*, a synthetic polymer with an unusually marked water-binding capacity, and *thihexinol methylbromide*, a parasympatholytic drug that exhibits a dominant action on gastrointestinal motor function.

Individually, both components have had a good deal of gastroenterologic study. Polycarbophil, the hydrosorptive component, was administered in oral dosages of 3 to 4 gm. for as long as two years without clinical or laboratory evidence of gastrointestinal irritation, systemic toxicity, or electrolyte imbal-

ance[1]. That it is a potent enteral hydrosorbent and a useful agent for symptomatic treatment of both diarrhea and constipation has also been demonstrated by controlled studies[2]. Orally effective dosage of thihexinol, originally identified as Sch 2868, was shown to produce pronounced inhibition of gastrointestinal motor activity[3] and to alleviate diarrhea in intestinal hypermotility states[3,4].

From his preliminary observations, Hock[5] concluded that the combination of polycarbophil and thihexinol is efficacious in the nonspecific treatment of chronic diarrheas. Gilbert and co-workers[6] noted that the two drugs, given together as Sorboquel, were effectively antidiarrheal in lower dosage than that

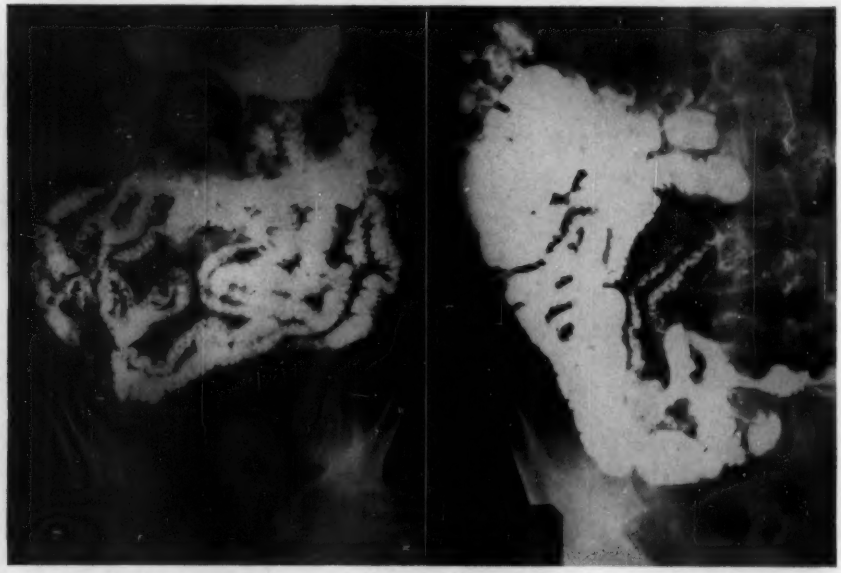

Fig. 2a Fig. 2b

Fig. 2a—One-hour control film. Barium has outlined the jejunum and has reached the ileum.
Fig. 2b—Three-hour control film. Barium has reached the hepatic flexure.

required with the use of either drug alone. The latter investigators stated that, since smaller amounts of the combined drugs are adequate for clinically satisfactory control of diarrhea, there is less chance that either component will cause dose-related side-effects.

Present Study

This investigation was concerned with a one-year evaluation of the use of Sorboquel in the nonspecific treatment of diarrhea. Clinical material consisted

of 65 private patients with relatively severe diarrheal disorders. With the exception of two patients whose diarrhea was due to acute gastroenteritis, all had histories of protracted diarrhea extending over periods of months to years. As would be expected, the irritable bowel syndrome accounted for almost half of the total cases of chronic diarrhea. The remaining cases were of organic origin, including mostly chronic ulcerative colitis and surgically short-circuited gastrointestinal states.

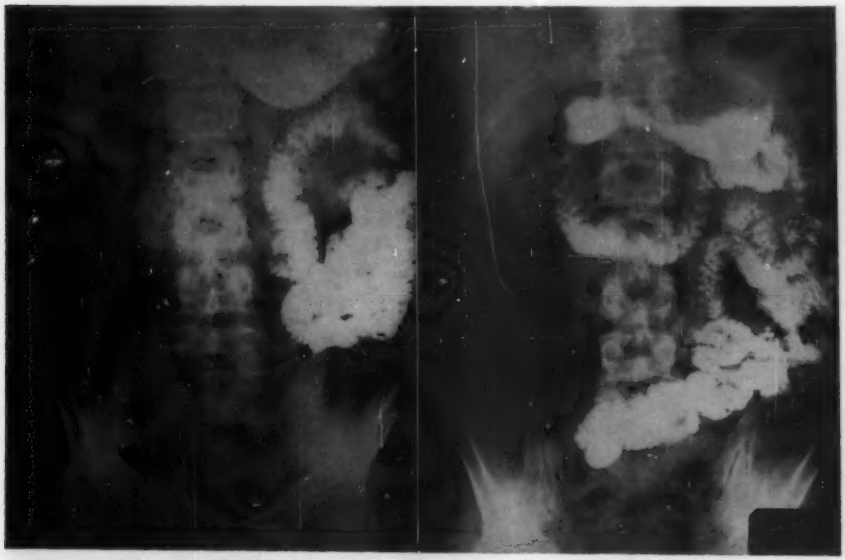

Fig. 2c Fig. 2d

Fig. 2c—One-hour control film after treatment with Sorboquel, 1 tablet q.i.d. Barium outlines stomach and upper jejunum.

Fig. 2d—Three-hour post-treatment film. Barium outlines jejunum and proximal portion of ileum.

Sorboquel tablets, supplied by the manufacturer*, contained 0.5 gm. of polycarbophil and 15 mg. of thihexinol methylbromide. Initially, most patients received a dosage of one tablet three or four times daily. When symptomatic control was achieved, it was usually possible to maintain the antidiarrheal effect with a reduced dosage of one or two tablets daily. The duration of treatment in this group of patients ranged from two weeks to 12 months.

*White Laboratories, Inc., Kenilworth, N. J.

Results

Clinically satisfactory control of diarrhea was noted in all but 3 of the patients with chronic diarrheal disorders (Table I). This order of symptomatic response to Sorboquel compares very favorably with that observed by others in comparable cases of chronic diarrhea[5,6]. Conversely, in the two patients with acute gastroenteritis, the drug was completely ineffectual.

The attainment of diarrheal control in all but 5 of the total group of 65 cases is noteworthy particularly since the drug was used with continued symptomatic relief in most patients for prolonged periods. Undoubtedly, one of the factors contributing to its usefulness for long-term therapy was the infrequent

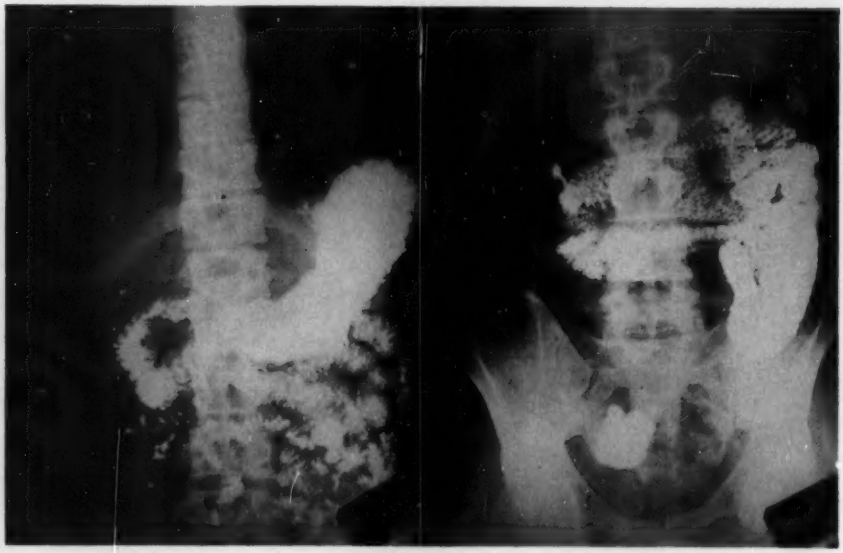

Fig. 3a Fig. 3b

Fig. 3a—Thirty-minute film. Barium is present in stomach and upper jejunum.
Fig. 3b—Two and a half-hour film. Barium has left stomach and is located largely in upper jejunum.

appearance of untoward reactions during the course of the study. Side-effects were limited to complaints of difficulty in urination in 3 patients, and of severe abdominal distention in another.

Several illustrative case reports follow:

Case 1:—G.N., a 23-year old white male, suffering from regional ileitis, had complained of diarrhea for two months. Figure 1a and 1b are reproductions of control x-ray films taken at 3 and 24 hours after the administration of

a barium meal. Figures 1c and 1d show 3-hour and 24-hour x-ray films approximately one month after institution of treatment with Sorboquel. Post-treatment abolition of intestinal hypermotility is most apparent in Figure 1d.

Case 2:—M.F., a 51-year old white male complained of diarrhea for six months following treatment with penicillin and chlortetracycline. Clinical work-up revealed a moderately severe case of postantibiotic enterocolitis. One-hour and three-hour control films (Figs. 2a and 2b) provide graphic evidence of hypermotility since the barium meal has reached the hepatic flexure at the end of the third hour. The post-treatment films, taken two weeks later, demonstrate the markedly retarded transit time after institution of Sorboquel therapy (Figs.

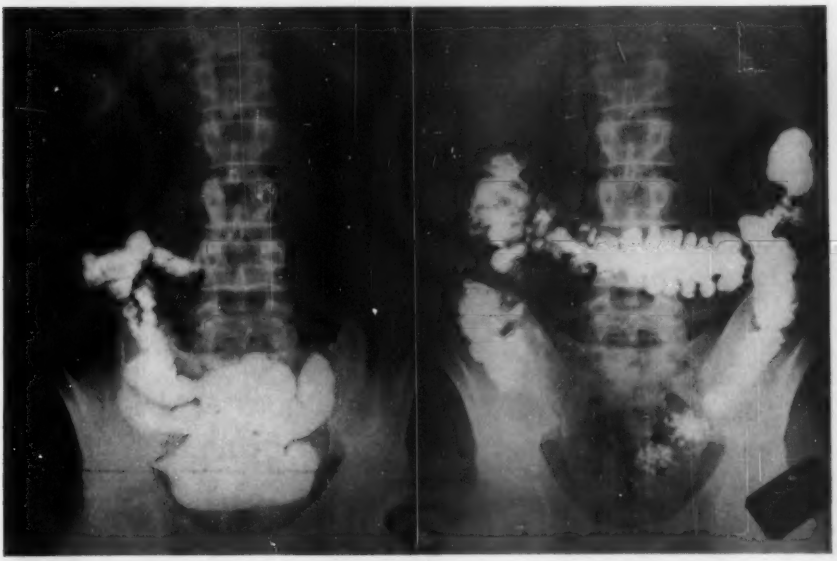

Fig. 3c Fig. 3d

Fig. 3c—Seven-hour film. Barium has advanced to terminal ileum.
Fig. 3d—Twenty-four-hour film. Barium outlines colon. Fluoroscopic examination at 48-hour interval revealed similar colonic pattern.

2c and 2d). At the end of the third hour, the barium remains mostly in the jejunum with little or no delay in gastric emptying.

Case 3:—W.C., a 30-year old white male with chronic diarrhea of functional origin. With administration of one Sorboquel tablet four times a day, the diarrhea was well controlled. X-ray studies of barium meal transit time were performed after the patient's symptomatic response to Sorboquel. Figures 3a to 3d reveal the gastrointestinal progress of the meal at the stated intervals.

Comment

Certain observations made during the course of this study merit further comment. The polycarbophil-thihexinol combination often alleviated diarrhea after other drugs, including opiates, had been ineffectual. Since one generally relies on the opiates for antidiarrheal therapy only as a last resort, the availability of an effective but less hazardous drug to control previously refractory diarrhea is worthy of emphasis. Noteworthy, too, is the observation that a maintenance dosage of only one or two Sorboquel tablets a day often proved adequate after the chronic diarrheal state had been brought under control with initially higher dosage of the drug.

TABLE I

Antidiarrheal Response to Sorboquel

	No. of Cases	Results	
		Good	Poor
Irritable bowel syndrome	28	27	1
Ulcerative colitis	13	12	1
Ileosigmoidostomy for ulcerative colitis	5	5	0
Ileostomy for ulcerative colitis	2	2	0
Regional ileitis	3	3	0
Diffuse jejunoileitis	3	2	1
Amebic colitis	2	2	0
Sigmoid diverticulitis	3	3	0
Intestinal polyposis	1	1	0
Sigmoid resection (carcinoma)	1	1	0
Acute gastroenteritis (viral)	2	0	2
Postantibiotic enterocolitis	1	1	0
Carcinoma of the pancreas	1	1	0
Totals	65	60	5

With respect to the x-ray studies of gastrointestinal transit in patients treated with Sorboquel, the demonstrated inhibition of jejunal motility without a marked delay of gastric emptying is remarkable. In our experience, such selective depression of enteral motor activity has not been produced by other antiperistaltic drugs. This selectivity of action may well explain the beneficial

effects of Sorboquel in the nonspecific treatment of intestinal hypermotility disorders of both organic and functional origins.

Summary

1. The use of Sorboquel, a combined enteral hydrosorbent and motility inhibitor, was evaluated for the nonspecific treatment of diarrhea in 65 cases of mostly chronic diarrheal disorders.

2. With initial dosage of 3 to 4 tablets a day, clinically satisfactory control of diarrhea was noted in all but 5 of the 65 cases.

Maintenance of symptomatic control was often possible with a dosage of 1 to 2 tablets a day. Side-effects were limited to the occurrence of dysuria in 3 cases and a complaint of abdominal distention in another case.

3. X-ray studies, following symptomatic response to Sorboquel therapy, demonstrated a marked suppression of intestinal hypermotility that was characterized by definite inhibition of jejunal motor activity without any pronounced delay in gastric emptying.

4. These observations support the conclusion that Sorboquel is a clinically safe and effective drug for the nonspecific control of relatively severe diarrheal states.

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CARCINOID TUMOR OF DUODENUM WITH MASSIVE HEMORRHAGE

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This case report is being presented because a carcinoid tumor of the duodenal bulb was responsible for a massive gastrointestinal hemorrhage. Although two cases have been reported in the literature[1] of massive gastrointestinal bleeding due to carcinoids of the small intestines, none of duodenal origin have as yet been reported.

In recent years more interest and attention have been directed to the subject of carcinoids. Sjoerdsma et al[2,3] have recently given a comprehensive re-

Fig. 1—Spot films of duodenal bulb. Note persistent radiolucent polypoid mass in bulb.

view of carcinoids and the role of serotinin in gastroenterology. A carcinoid tumor of the duodenum is in itself a rather rare finding. Over a 28-year period, from 1928 to 1956 only four cases were reported[4] in a group of 21 carcinoids. A survey of 356 carcinoids[5] revealed the presence of eight carcinoids in the duodenum. Furthermore, carcinoids found in the gastrointestinal tract, outside of the appendix, are more apt to be malginant and metastasize. From a pathological point of view the case in question was benign. The rarity of massive bleeding resulting from a duodenal carcinoid tumor prompted this report.

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Case Report

B. H., a 65-year old, white female housewife was admitted to the hospital the evening of 23 October 1959 because of severe upper gastrointestinal bleeding. The day before admission she had mild epigastric discomfort unrelieved by home remedies. That morning she had a sudden episode of hematemesis and syncope. This recurred in the afternoon and was accompanied by chest pain. That same evening with increasing signs of blood loss she was hospitalized.

There was no previous history of dyspeptic symptoms.

Past history:—The patient was known to be a moderate hypertensive for many years. She had had a coronary occlusion ten years previously. Seven months prior to admission she was found to have a mild diabetes, which was controlled by a low calorie diet.

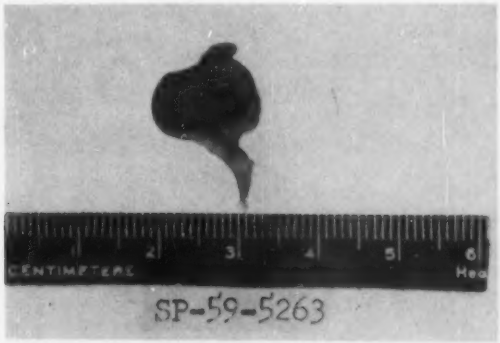

Fig. 2—Gross specimen of the duodenal carcinoid tumor.

Physical examination:—The patient was a well developed, well nourished elderly female, conscious, acutely ill with the usual signs of marked blood loss—pallor, weakness, dyspnea, cold perspi n tachycardia. Pulse was 120; temperature, 98.6; blood pressure, 160/82. neart sounds were regular, no murmurs. Lungs were clear to auscultation and percussion. Abdomen—liver and spleen were not palpable. There was no localized tenderness; no palpable masses. Bowel sounds were active. Pelvic and rectal examinations were negative. The remainder of the examination was essentially negative.

A Levin tube was inserted soon after admission and revealed the presence of frank blood.

Laboratory data:—Hematocrit upon admission was 19.5 gm. ECG indicated chronic myocardial alterations. Subsequent blood chemistries were within normal limits, except for a slightly elevated blood sugar.

The admitting impression was that of an upper gastrointestinal hemorrhage secondary to either a duodenal or gastric ulcer. Neoplasm was to be considered.

Hospital course:—Immediate steps were taken to replace loss of blood and combat anoxia. She received four units of whole blood and packed red cells. Oxygen was given for dyspnea and anoxia. The patient improved and when oral feedings were possible she was put on a Sippy diet and antacids. The patient's hemic component improved and the blood stabilized.

On 27 October, four days after admission, an upper gastrointestinal x-ray series was done. The esophagus and stomach were normal. The duodenal cap was somewhat defective and there was a faint suspicion of a small polyp. A recheck gastrointestinal series a few days later, with spot films of the duodenal cap (Fig. 1) indicated a small polypoid mass in the duodenal bulb. Surgical

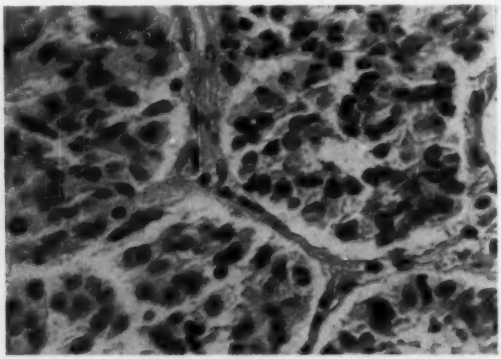

Fig. 3—Photomicrograph, high power, of cross section of carcinoid tumor.

intervention was deemed advisable. The patient made an uneventful postoperative recovery.

Surgical report:—"On palpating the first portion of the duodenum, just distal to the pyloric vein on the anterolateral surface, a nodule measuring approximately 1 cm. was felt within the lumen. This was firm and moved slightly. The polypoid mass was visualized after duodenotomy. There was no stalk and the tumor was sessile. It was excised together with the surrounding portion of the normal mucosa."

Pathologist's report:—Specimen (Fig. 2) consists of a rather oval portion of soft tissue said to be removed as a duodenal polyp. It measures .9 cm. in diameter. The external surface contains in one area a hemorrhagic area measuring 9.3 mm. in diameter, at the center of which a pin point, dark area is present. On section of the specimen the cut surface is greyish brown in color and slightly hemorrhagic in the center.

Microscopic:—Preparation consists of portion of duodenum. There are small, irregular solid masses of cells scattered throughout supported by a scant amount of stroma. These cells show poorly defined cytoplasmic borders and dark staining nuclei. Many of the cells show vacuolated cytoplasm. Focal areas of round cells are noted. The tumor appears to be well encapsulated.

Diagnosis:—Carcinoid tumor. (Figs. 3 and 4.)

Summary

1. A case of massive gastrointestinal bleeding due to carcinoid of the duodenum has been presented.

2. The presenting symptom of massive gastrointestinal bleeding from this entity is unusual.

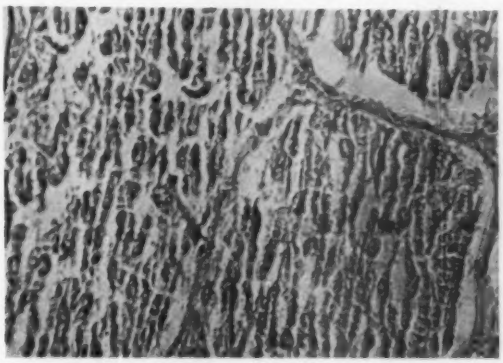

Fig. 4—Microphotograph of carcinoid tumor after silver staining (argentaffinoma).

3. Roentgenologically a "polypoid mass" in the duodenal cap was suspect prior to operation. This proved to be an eroded benign carcinoid tumor. Clinically there were no symptoms of the "Carcinoid Syndrome".

4. We have presented this case as an additional, rarer cause of upper gastrointestinal bleeding.

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"PEPTIC" ULCER: THE CAUSE OF THE DEFECT

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"The advance of Medicine has at all times been impeded by two factors; by the existence of so-called authorities, and by the existence of fashionable medical theories."

Rudolf Virchow

It is obvious that this aphorism pertains to much of the current thinking on "peptic" ulcer, but it is even more obvious that it should not be so. When we sit down before the facts, we find many more than were available to John Hunter and Jean Cruvelhier; yet their questions about the "digestion of the stomach" have not been answered. When we look for the "durable results of the perishable years", we search almost in vain; ulcers of the gastrointestinal tract are increasing in numbers decade by decade and the recurrence rate seems oblivious to our protestations of knowledge. Despite the large number of investigators, there are no experts and despite the grand array of theories, none is fashionable enough to be acceptable.

When Francis Bacon strode into the intellectual life of the world, he found only a few lights shining through the gloom of the Dark Ages–dark because of the magic of an unvarying creed of philosophy and religion. Since the terrible year that saw the death of Alexander, Aristotle, Demosthenes and creative thinking, the world had dozed. Bacon attempted to awaken it by presenting to us his priceless gift–the scientific method of inquiry. His first admonition, however, was that the thinking man must become innocent of abstractions, must wash his thoughts clean of preconceptions and must abolish prejudices. Man first had to destroy the "Idols of the Mind"–the thoughts mistaken for things. Only then could he be ready to use the scientific method which was to light his path out of the centuries of darkness.

It is time for us to approach the ulcer problem with minds free of fixed ideas. Those who have suggested such freedom have generally been ignored, despite our ignorance and our failure to cure or even control ulcer disease. It remains "peptic" ulcer with all of the connotations of the term which pertain to genesis. Before embarking upon new seas of research in the gastrointestinal juices, we might pause to consider whether ulceration of the mucosa might arise from disease or disturbance within or beneath the mucosa itself. This idea has appeared often in the medical literature but it has found itself the basis for scientific inquiry only infrequently. Most authorities pay lip-service to the

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"mucosal factors", but the mucosa lies nearly untouched in the search for information about "peptic" ulcer. It seems probable that the "acid-pepsin" keystone in current thinking–promulgated by authorities and supported by fashionable theories–has done little but impede the advance of medicine in this field. To those who dismiss as useless any consideration of "peptic" ulcer without study of acid-pepsin, a word or two from Spencer is offered: "There is a principle which is a bar to all information, which is proof against all arguments, and which cannot fail to keep a man in everlasting ignorance; this principle is–contempt prior to investigation". It may be necessary to be bold, but boldness and discipline are tools of the scientific mind.

". . . and now remains that we find out the cause of this effect; or rather say the cause of this defect, for this effect defective comes by cause". Polonius, puzzled by Prince Hamlet's sudden madness, recognized well the importance of finding the cause rather than observing the effects. The difficulty or the patience required in the search for the cause of mucosal disease must not persuade us to rest forever on the unsound foundation of secretions. Enough clinical observation and experimental work are available to make it abundantly clear that normal mucosa does not ulcerate. The extraordinary localization and constancy in size of duodenal ulcers and the pattern of gastric involvement in ulcer disease lead us inexorably to the mucosa as the site of the primary pathology. The process of ulceration must begin with local loss of viability of groups of mucosal or of submucosal cells. The gaze of our inquiry must be fastened upon the gastrointestinal mucosa. Once focal devitalization of the mucosa has occurred, acid-pepsin can readily digest and excavate the gut wall. Our search, then, must be for a mechanism that can produce discrete tissue damage in certain specific locations.

To ensure that our gaze will not stray from this focal destruction of mucosa, the concept of a "Final Common Pathway" has been applied to the problem of ulcer genesis. This final common pathway must be visualized as the physiological or pathological mechanism which, once set in operation, leads inevitably to destruction of mucosal cell viability in a specific area. The process itself must obviously be a physicochemical alteration within the cell. Our thinking, observation and research must be devoted to identification of the final common pathway and to an elucidation of the stimuli that initiate its action. This simple concept can serve as a guide to our thinking and to proposed research if we make it a *sine qua non* for every general theory of ulcer genesis–no theory can be considered adequate unless it includes a set of directions telling us how to go from the particular stimulus under consideration to the final common pathway. Surely "stress" and psychic disturbances play a role in the development of ulcers, but the major theoretical problem–the development of hypotheses–is to trace these "stress" responses or psychic influences to the final common pathway. If this seems immoderate, let us take heart from Harvey's brave words: "Nature is herself to be addressed; the paths she shows us are to be boldly

trodden; for thus, and whilst we consult our proper senses, from inferior advancing to superior levels, shall we penetrate at length into the heart of her mystery."

In addition to its ability to influence cellular integrity, the mechanism for which we are searching must have the following characteristics: it must participate in generalized body responses but must be capable of localizing its influence; it must be influenced by the "stress" response; it must be receptive to psychic phenomena; it should be independent of other gastrointestinal functions and it should represent a malfunction of some physiological process. None but the vascular system can meet all of these criteria; no other system is so important in the maintenance of cell life. Thus we must look upon the vascular tree as a primary ulcerogenic pathway leading from diverse stimuli to the final common pathway. Numerous attempts have been made to incriminate the vascular system in the genesis of ulcer but, in the past, an insufficient knowledge of the anatomy of the vascular bed of the gastrointestinal tract has vitiated these theories. Only recently have careful anatomic studies been performed on the blood supply to the gastrointestinal mucosa. These studies have been reinforced by *in vitro* and *in vivo* experiments on the intact circulatory system and it is now clear that there does exist an extensive submucosal plexus of both arteries and veins communicating freely with each other through a network of anastomoses. A similar arrangement is present on the glandular side of the muscularis mucosae as well. This would make it virtually impossible for arterial occlusion to play any part in the destruction of vitality of any portion of the mucosa. Such a system, however, which is under both neural and hormonal control, makes it possible for large amounts of blood to be shunted away from the nutrient capillary network directly into the venous system under conditions which allow the shunts to be fully opened. On the other hand, if the shunts are closed, all of the arterial blood will pass through the capillary system. It is readily evident that such a physiologic mechanism under abnormal conditions might be capable of modifying the blood supply to a localized area of mucosa. That is actually does so remains to be proved, but the problem is stated.

The next step is the determination of the final common pathway itself. A circulatory disturbance would seem to be a common path by which varied stimuli are transmitted to the mucosa and the results of such a disturbance would be the final step which would inevitably lead to important physicochemical alteration of the cell. Surely, hypoxia is the most obvious result of circulatory inadequacy and it may well be the final common pathway which we are seeking. There are, however, many other functions of the circulation which are related to tissue life and health and none of these can be ignored in our search.

It can be seen that this approach is nothing more than a plea for logical investigation of the means whereby ulcerogenic influences can influence the

vitality of a small group of cells in a specific location in the stomach or the duodenum. Good investigation does not require the investigator to carry out his calculation to the fourth decimal place nearly so much as it requires him to use a technic now 340 years old—the scientific method. This is the road—the pathway—on which we will find the cause of the defect.

President's Message

I wish to thank the membership for the honor bestowed upon me as your President for the coming year. With the cooperation of the officers and members I hope to make this a banner year.

There are certain suggestions in our fields of endeavor which I believe would be beneficial to our organization and to its members.

On the whole our conventions have been of a high caliber and quite successful, but we must always strive for improvement. We should make an effort to get the best talent available in order to improve the quality of the papers, even if this would involve substantial additional expenditures. In the long run, this will prove profitable by increasing the membership and the attendance at the conventions.

I would advise that the Postgraduate Course be conducted on a seminar basis. The purpose of this is to encourage active and informal participation among all who attend, and thus will make the course more interesting and informative to each individual member. I feel sure that this will increase the registration for the courses.

I also strongly favor the recommendation to hold at least one regional meeting per year in each of our four established areas. By pooling their efforts, the Governors in these four areas can make these meetings successful.

This will provide the membership with a refresher course as well as the latest information in our specialty. It will permit those, who because of great distances are not able to attend every annual convention, an opportunity to meet with other members of the College in and around their area. It will also enable the Governors to enroll more members, in our organization.

Henry Baker

ABSTRACTS FOR GASTROENTEROLOGISTS

ESOPHAGUS

CARCINOMA OF THE ESOPHAGUS AND CARDIA: F. Henry Ellis, Jr., Robert C. Jackson, Julius T. Krueger, Jr., Herman J. Moersch, O. Theron Clagett and Robert P. Gage. New England J. Med. 260:351 (19 Feb.), 1959.

All cases of carcinoma of the esophagus and cardia, 909 in all, encountered at the Mayo Clinic between 1946 and 1956 were reviewed to determine whether resective surgery was of sufficient benefit to the patient in terms of relief of symptoms and prolongation of life to justify the risk and the expense and discomfort of a major operative procedure. To determine whether improvement in clinical management occurred with experience the cases were further divided into two groups, those seen in the five-year period 1946 through 1950 and those seen in the five-year period 1951 through 1955. Surgical exploration was carried out in 45.6 per cent of the patients. Resections were done in 27 per cent of the cases, but a curative resection was done in only 20.8 per cent. Palliative resection was done in 6.2 per cent. A wide variety of curative and palliative procedures were employed.

There were 48 hospital deaths (11.6 per cent) among 414 patients who underwent operation. The mortality for patients undergoing resection was 15.9 per cent. Nearly 50 per cent of the deaths were the result of leaking anastomoses. Comparison of the two five-year groups showed a definite improvement in the hospital mortality, dropping from 20.4 to 13.2 per cent despite a higher resectability in the latter period. An increase in the number of resections carried out on patients with carcinoma of the lower portion of the esophagus or carcinoma involving the esophagogastric junction accounted for the increased resectability rate in the latter period.

The over all five-year survival rate was 17.2 per cent in patients surviving resection. Squamous-cell carcinomas of the lower part of the esophagus and esophagogastric junction have the best prognosis, and carcinomas of the upper half of the esophagus and adenocarcinoma involving the esophagogastric junction have the worst prognosis. Radiation therapy did not favorably affect the survival of patients in whom resection was not done, with possible exception of those with lesions in the cervical portion and upper half of the esophagus.

In spite of the low five-year survival rate (3.9 per cent of *all* patients seen) the authors feel that there is some hope in the analyses of the presented data. A better survival rate might be achieved by reduction in the mortality of resection, by an increase in the operability rate and, above all, by proper selection of patients for operation.

LOUIS A. ROSENBLUM

THE NATURAL HISTORY OF ESOPHAGEAL VARICES: L. A. Baker, C. Smith and Gerald Lieberman. Am. J. Med. 26:228 (Feb.), 1959.

An analytical study has been made of the clinical course, uninterrupted by surgery, of 115 cirrhotic patients in whom the diagnosis of esophageal varices was established prior to any bleeding. These patients were followed for intervals varying from one to six years.

Of the 115 patients, 41 were living and 75 were dead at the time the data were assembled. Bleeding occurred in 28.6 per cent; 17.3 per cent died of exsanguination, 26 per cent died of hepatic failure, and 20 per cent succumbed to unrelated causes. Death from exsanguination during the first episode of bleeding occurred in 9.5 per cent. Approximately 90 per cent of the deaths from liver disease occurred within two years after varices were diagnosed.

Knowledge of these aspects of the natural course of such patients is necessary before it is possible to know what must be accomplished by routine prophylactic shunt surgery in order to establish the validity of this surgical policy. It does not seem that a present routine prophylactic decompression surgery offers any definite advantage to the patient.

JOHN M. MCMAHON

STOMACH

CHRONIC GASTRITIS: Emmanuel Deutsch and Howard J. Christian. J.A.M.A. 169:2012 (25 April), 1959.

In planning an adequate program for treatment of chronic gastritis, a satisfactory method is urgently needed with which to obtain objective evidence for correlation with clinical symptoms of gastric inflammation. The use of gastroscopy and multiple biopsies has enabled formation of a definitive plan for management of the problem.

The biopsies show that in severe chronic gastritis the mucosal pattern is distorted by irregular distribution of the gastric glands, increased numbers of mucus-secreting cells, and inflammatory infiltration of the stroma. The pattern of symptoms (pain-food-pain cycle) and failure to respond to antacids also distinguish chronic gastritis from the typical peptic ulcer. Ninety-two patients with chronic gastritis were treated with bed rest, sedatives, gastric suction, meals planned not to exceed the patients critical volume, and a combination of aluminum hydroxide gel with oxethazaine hydrochloride, a topical anesthetic. While the severe forms of chronic gastritis were refractory to this treatment, the moderate and mild forms proved amenable, and the combination of antacid and anesthetic afforded relief from pain for periods up to six hours after each dose. Medications were continued for six days to 18 months without evidence of significant side-effects.

SAMUEL M. GILBERT

THE MANAGEMENT OF THE COMPLICATED DUODENAL ULCER: Joseph Shaiken. Wisconsin M. J. 58:215 (April), 1959.

The author considers the diagnosis and treatment of the three most common complications of ulcer:

Hemorrhage—The diagnosis depends on the history, fluoroscopic and roentgen study of the upper digestive tract is done within a few days depending on the condition of the patient. Bromsulfalein determination helps to rule out bleeding esophageal varices due to cirrhosis of the liver. Esophagoscopy and gastroscopy are utilized in indicated patients. Patients in whom operation is apt to be required are: 1. the patient who has stopped bleeding while under treatment in the hospital and then starts to bleed again, 2. patients in the older age group, 3. if pain is present in addition to hemorrhage, 4. the presence of a postbulbar ulcer, and 5. massive hemorrhage and the danger of exsanguination.

Obstruction—This is of two types: 1. Transient, due to spasm, edema, and inflammation. Treatment: No food by mouth, gastric aspiration, intravenous fluids, and antispasmodics by injection. The aspirations are carried out daily, measured and chart-

ed. If the amount of aspirated material becomes greatly decreased promptly, it is evident that obstruction is subsiding. 2. Permanent obstruction due to duodenal scarring: The gastric content does not show a rapid reduction in amount. This may be corroborated by fluoroscopy of the stomach at 6, 12 and 24 hours. (The stomach is first emptied of fasting contents.) If permanent obstruction is present, the stomach is decompressed by drainage, fluid is replaced intravenously, and electrolytic balance is maintained. The surgical treatment of choice is subtotal gastrectomy.

Perforation—This is chiefly of two types: 1. Acute free perforation; the symptoms are severe abdominal pain and collapse, with a board-like rigid abdomen. Treatment: Nonoperative; the author advises nonoperative treatment for perforations that have occurred many hours before or in a patient who is in very poor condition. Gastric aspiration, parenteral fluids, antibiotics, and careful observation of the patient are employed. Operative: This is employed in the vast majority, and consists of simple closure or subotal gastrectomy in a younger patient. 2. Walled-off perforation (confined perforations)—In this type, the base of the ulcer is formed by a neighboring organ, usually the pancreas or liver. The symptoms consist of a change in ulcer pattern. The pain becomes more constant, more severe, and may require opiates for relief. Often the pain radiates to the anterior chest wall, back, or lower abdomen. Treatment: Hospitalization and intensive medical treatment are required. Often the response is poor and surgical treatment is necessary.

SAMUEL L. IMMERMAN

FATAL HEMORRHAGE FROM DUODENAL VARIX: Paul Hwang, Eugene J. Jorgenson, Paul Anspach and Albert F. Brown. J. Internat. Coll. Surgeons 31:414 (April), 1959.

Intestinal varix as a cause of massive hemorrhage is not a commonly encountered situation if the term varix is restricted to the usual concept of a chronically distended nonangiomatous vein of macroscopic caliber. In the described case, the lesion appeared to correspond both morphologically and pathologically to a venous varicosity. Internal varices may occur in any one of many sites, wherever there is a sustained increase in venous pressure from any of several causes. The compression and constriction of anastomotic veins caused by trauma or thrombosis when associated with familial inherent weakness, for example, leads to varicosity. The development of internal varices is difficult to establish. The authors suggest that when massive intestinal hemorrhage is associated with probable portal hypertension, external varicose veins or history of other venous anomaly, the rupture of an intestinal varix should be included in the differential diagnosis. Particularly, when abdominal visceral or parietal varices are encountered during exploration in such a case, the intestine should be carefully searched for a site of possible varicose rupture.

BERNARD J. FICARRA

CONGENITAL POSTEROLATERAL DIAPHRAGMATIC HERNIA: PATHOGENESIS AND TREATMENT: Virul Kao Borisuti and Smarn Muntarbhorn. J. Internat. Coll. Surgeons 31:401 (April), 1959.

This report emanates from Thailand and concerns a new born boy and a new born girl with congenital diaphragmatic hernia. Clinically this type of hernia is diagnosed by the signs of dyspnea, cyanosis and dextrocardia. The heart signs are best heard on the right side owing to the mediastinal shift to the right. X-ray studies are essential for an exact diagnosis. Coils of intestine are seen on a simple film. If there is a suspicion that the intestine may be confused with congenital pulmonary cysts, the use of barium prior to taking the x-ray will categorize the lesion. The ideal management of this entity is to operate early in order to redeposit anatomical structures into their proper locations. The early demise of children with this pathological state is due to associated abnormalities—especially pulmonary hypoplasia.

BERNARD J. FICARRA

INTESTINES

A NEW STUDY OF INTESTINAL OBSTRUCTION WITH SPECIAL REFERENCE TO CASES INVOLVING DELAYED TREATMENT: M. S. Emine. J. Internat. Coll. Surgeons 31:407 (April), 1959.

The surgeon presents his experience on intestinal obstruction in various hospitals in Tabriz, Iran. He states that the predisposing cause of this entity appears to be a dietary one. The author believes that a diet consisting of too much bread of heavy quality, together with excessive use of such liquids as the so-called "dough" (a mixture of yogurt and water). Other dietary errors also contribute to this illness. The principles of treatment for intestinal obstruction are outlined with emphasis on the urgent need of good preoperative care, particularly when treatment has been delayed for several days. This care must include all routine precautions, plus any special procedures required in the individual case, since the patient who has delayed treatment is usually in poor condition. Management prior to surgical intervention, therefore, should be governed by the adage "make haste slowly". Athough the operation must be considered an emergency procedure, adequate preparation by effective modern means remains vitally important.

BERNARD J. FICARRA

CANCER OF THE LOWER LEFT COLON AND RECTUM: James D. Hardy. Am. Pract. & Digest. Treat. 10:613 (April), 1959.

The author emphasizes the controversy that is still existent over the handling of lesions lying in the rectum in the region between 6 cm. above the dentate line and the pelvic floor (8-10 cm. above the dentate line). He quotes the Mayo Clinic with a 50.8 per cent five-year cure rate for lesions in this area treated by anterior resection and a 54.8 per cent cure rate treated by combined abdominoperineal resection. The small difference in cure rate in their minds does not justify leaving a patient with a colostomy. The author, however, leans more to abdominoperineal resections in this disputed area. The over all resectability rate of lesions of the colon and rectum approaches 90 per cent with a cure rate of 50 to 60 per cent. No dispute exists for the treatment of lesions below 6 cm. above the dentate line by abdominoperineal resection and anterior resection for those lesions above the pelvic floor. In the past decade an awareness of implantation of cancer cells in the line of anastomosis, frequency of blood stream emboli, presence of multiple cancers of the colon (5 per cent) and adjuvant chemotherapy has led to the adoption of the use of tape around the bowel prior to resection and anastomosis, ligation of the main blood supply prior to the handling of the tumor, thorough exploration of the rest of the bowel and cauterization and removal of polyps and tumors along with chemotherapy in certain cases. The role of polyps in the little understood etiology of cancer of the colon is questioned and two completely divergent opinions are quoted. However, it is felt that invasive cancer increases with the size of a polyp being less than 1 per cent in polyps 1 cm. or less in diameter and more than 9 per cent in those 1½ cm. or over in size. In general, it is felt that removal of polyps is an urgent cancer prophylactic.

JULES D. GORDON

NEWER DEVELOPMENTS IN PROCTOLOGY: Alfred J. Cantor. Am. J. Proct. 10:116 (April), 1959.

Proctology is a relatively new specialty but its scope is wide. A proctologist must not only be familiar with the lower end of the rectum and anus but with the patient as a whole. In this paper the author touches on various subjects as they relate to the colon.

The author stresses ambulatory proctology which makes it possible for the average patient to return to work within 24 or 48 hours after surgery with markedly reduced frequency of complications.

A. J. BRENNER

RECTAL SUPPOSITORIES: THEIR USE IN INTERNAL MEDICINE: Lester S. Blumenthal and Marvin Fuchs. Am. J. Proct. 10:130 (April), 1959.

Rectal suppositories are an important vehicle for giving patients quick relief from certain maladies. Since absorption through the rectal mucosa is more rapid than through the upper gastrointestinal tract only ⅓ the dose is generally required. Where the hypodermic needle is not available for quick relief in asthma, migraine headaches, severe nausea and vomiting, severe pain and insomnia, the suppository is of extreme value. Rectal suppositories are also useful for the treatment of local conditions such as fissures, infectious and inflamed hemorrhoids. In children and in some adults simple glycerine suppositories may be useful to initiate bowel movement.

A. J. BRENNER

LIVER AND BILIARY TRACT

REPAIR OF INJURY TO THE COMMON BILE DUCT: George L. Hoffmann and George Crile, Jr. Cleveland Clin. Quart. 25:126 (July), 1958.

The report is based on a survey of the results of 69 operations performed for repair of injuries to the common bile duct.

The authors utilized several technics and concluded that hepaticoduodenostomy gave results which were better than those of other methods. The simplest approach was then a subcostal incision, the suture material of choice was fine chromic catgut and the best splint a standard T-tube.

THEODORE COHEN

THE RELATION OF CHOLECYSTECTOMY COMPLICATIONS TO INADEQUATE EXPOSURE AND TECHNICAL ERRORS: John T. Sullivan, Jr. Illinois M. J. 114:156 (Oct.), 1958.

The author clearly points out that a patient finds little comfort and satisfaction in the knowledge that his particular complication occurs only one per cent of the time. In this article, the author directs attention to those things responsible for the complications after cholecystectomy. It is pointed out that the average length of life in the patient with unsatisfactory cholecystectomy is about one-fourth as long as that of patients having a good postoperative result.

The technical errors which lead to complications are: inadequate skin incision with resultant inadequate exposure; a lack of planned method of visceral retraction; a lack of recognition of abnormal regional anatomy; failure to explore the common duct when so indicated; or failure to explore the sphincter of Oddi by transduodenal approach. The author feels that three other errors of surgical technic which lead to lesser complications are: failure to correctly ligate the cystic duct, failure to reperitonealize denuded areas, and lastly, failure to perform an adequate abdominal exploration when conditions permit.

The errors in surgical technic which lead to disastrous complications are enumerated in this article as well as those complications which are preventable.

It is the conclusion that cholecystectomy is still a major surgical procedure and that the morbidity and mortality rates in spite of their marked improvement in the past years can still be further reduced if the operating surgeon possesses ability to meet any situation incident to biliary tract surgery.

L. K. BEASLEY

OBSERVATIONS ON ANTIBIOTICS IN THE TREATMENT OF HEPATIC COMA AND ON FACTORS CONTRIBUTING TO PROGNOSIS: James M. Stormont, Joseph E. Mackie and Charles S. Davidson. New England J. Med. 259:1145 (11 Dec.), 1958.

The authors studied 68 patients with hepatic coma or precoma. Of these, there were 60 cases of cirrhosis of the liver (alcohol type), 5 postnecrotic cirrhosis, 2 with

hemochromatosis, and 1 with metastatic carcinoma of the liver.

The treatment included general measures such as correction of blood loss, esophageal tamponage when indicated, elimination of infection, fluid replacement, vitamin supplementation, and withdrawal of drugs known to predispose to hepatic coma. The initial therapeutic measures included the elimination of protein from the patient's diet, and giving a mixture of high dextrin carbohydrate (available as dextrin) and fruit juices, providing at least 1,500 calories per day. In addition, neomycin or paromomycin and chlortetracycline (Aureomycin) was administered. Then the protein was reinstituted in the form of whole milk, or sodium-depleted milk, with the high dextrin carbohydrate on the second to the fourth day. Under this treatment, the authors observed an improvement in 71 per cent of the patients. They pointed out that a serum bilirubin concentration over 20 mg. per 100 ml., and a serum sodium concentration under 130 mEq./l., were the most serious prognostic laboratory observations. Of interest among their cases, were 28 patients presenting a renal insufficiency terminally, due to various causes. Of the 29 autopsied cases of cirrhosis, 52 per cent revealed disease of the gallbladder or pancreas or both. They believe that their method of treatment was found to be superior to other procedures utilized heretofore.

ZACH. R. MORGAN

PRODUCTION OF IMPENDING HEPATIC COMA BY CHLOROTHIAZIDE AND ITS PREVENTION BY ANTIBIOTICS: Joseph E. Mackie, James M. Stormont, Robert M. Hollister and Charles S. Davidson. New England J. Med. 259:1151 (11 Dec.), 1958.

The authors report on a study of five cases with cirrhosis (alcohol) and ascites, with the production of an impending hepatic coma following the administration of chlorothiazide, a nonmercurial diuretic agent; and its prevention by the oral administration of broad-spectrum nonabsorbable antibiotics.

None of the 5 patients presented any clinical evidence of impending hepatic coma during the premedication control period. Chlorothiazide was administered to these patients and signs of impending hepatic coma was observed. In addition, there was a rise of arterial ammonia concentration, increased sodium and potassium excretion, and a fall of serum potassium concentration.

After cessation of the drug, recovery occurred in from 24 to 72 hours. In several instances an antibiotic (paromomycin) was given, which seemed to hasten the improvement.

The etiological factors involved in the production of hyperammoniemia following the use of chlorothiazide is undetermined.

ZACH. R. MORGAN

LIVER DISEASE IN DURBAN AFRICANS: Theodore Gillman, Michael Hathorn and N. M. Lamont. South African J. M. Sc. 23:187 (Dec.), 1958.

It has previously been shown, that there is a high incidence of liver disease among Africans. This report discusses the histopathological findings in liver-biopsy specimens obtained from 200 African male adults.

One hundred cases were first selected from individuals with either palpably enlarged liver or the presence of ascites suspected of a hepatic origin. The second 100 cases selected showed clinical criteria which —based on the study of the first 100 cases— were suspected to be associated with hepatic siderosis and/or cirrhosis.

Siderosis was found in 88 per cent of the patients, 71.5 per cent being of an advanced nature. Portal fibrosis occurred in 43 per cent of the patients and portal cirrhosis in 18.5 per cent. Portal cirrhosis was closely correlated with advanced portal siderosis. This suggests that the presence of iron in the portal tract may be fibrogenic in these patients.

HANS J. JOSEPH

SPLEEN

PERCUTANEOUS SPLENOPORTOGRAPHY IN PORTAL HYPERTENSION: Benjamin H. Sullivan, Jr., Robert H. Herman and John E. Myers, Jr. U. S. Armed Forces M. J. 9:1257 (Sept.), 1958.

Portal obstruction may arise from obstruction outside the liver or from intrahepatic causes. Postcaval shunts are indicated in esophageal varices, but cannot be done if portal vein is thrombosed. X-ray visualization of the portal vein and its tributaries is important to determine the site of obstruction, so as to know proper operative procedure. The authors have been using splenoportography as a preoperative study of patients with portal hypertension.

Demerol, 75 mg. is given i.v. together with a 1 ml. test dose of 50 per cent Hypaque. Epenephrine and Nalorphin should be available to counteract adverse reactions. By percussion and palpation of the spleen, a site for insertion of the needle is selected, usually in the left mid axillary line or posterior axillary line at the 8th or 9th intercostal space. Skin is prepared and infiltrated with novocain and patient told to hold his breath in mid inspiration. A No. 18 needle, spinal type, is inserted into the spleen. A flow of blood indicates the needle is in the splenic substance. Patient should not breathe while needle is being manipulated or splenic capsule may be torn. After needle is in, patient may resume shallow breathing. Splenic pressure is measured by a saline-filled manometer connected to the needle by a polyethylene tube, over 200 saline solution is high. The splenoportogram is made by injecting 25 ml. of 50 per cent Hypaque rapidly through the needle into the spleen. The needle is removed and x-ray exposures made over a 12-second period using a Schonander bi-plane film changer. After the procedure patient is not moved but returned to bed gently on a litter. He is kept flat in bed for 6 hours and then for 24 hours, after which he can sit up. Pulse and blood pressure are measured frequently for the first 6 hours.

The authors then present 5 cases with radiographic demonstration of the spleen.

In their discussion the authors summarize the reasons for failure of splenoportogram demonstration:

1. Inability to inject dye into the spleen because of faulty needle placement.
2. Subscapular infiltration of the dye, even if the dye was supposed to be injected into the spleen.
3. Technical failure of radiographic equipment.

Indications for splenoportography are:

1. Determination and measurement of portal hypertension.
2. Allow preoperative selection of proper surgical shunt operation.
3. To properly evaluate shunt function at later dates.
4. As a diagnostic aid in the evaluation of hepatic tumors, obscure splenomegaly, ascites, congenital portal venous anomalies, portal vein thrombosis and gastrointestinal hemorrhage.

LOUIS K. MORGANSTEIN

TRAUMATIC RUPTURE OF THE NORMAL SPLEEN: Warren W. Francis and Jorge Benavides. Rhode Island M. J. 42:102 (Feb.), 1959.

The authors discuss diagnosis and treatment of rupture of the spleen as exemplified by a series of 30 patients with traumatic rupture. They stress that 93 per cent of the cases are associated with nonpenetrating trauma and note that only 20 per cent were associated with auto accidents. In addition to the usual abdominal pain associated with tenderness and spasm involving primarily the left upper quadrant 53 per cent of their patients complained of shoulder pain while 73 per cent showed some evidence of shock. In only one patient was a mass palpable. A high percentage of the cases had a white blood count over 10 thousand, while only 30 per cent had a hemoglobin below 10 gm. X-ray aided diagnosis in showing evidence of an elevated left leaf diaphragm, obliteration of the splenic shadow with serration of the greater curvature of the stomach, of a left upper quadrant mass with or without displacement of abdominal organs. The authors stress that diagnostic peritoneal tap is important in diagnosis of splenic rupture and if blood is found, is almost pathognomonic. Negative tap, however, should

not delay operation if the other signs point towards either a primary or delayed type of rupture. There were no deaths in 28 operative cases in which splenectomy was performed. Splenectomy in this series, as in most, is obviously the treatment of choice, when the diagnosis is made. The technic of diagnostic peritoneal tap is carefully described. Diagnostic peritoneal tap is not completely without danger, but no accidents were reported in this series.

RALPH EICHHORN

PATHOLOGY AND LABORATORY RESEARCH

STUDIES ON BILE PIGMENT IN BILE. III. BILIRUBIN CONTENT OF BILE IN DOGS WITH PATHOLOGICALLY CHANGED BILIARY TRACT: Tomonobu Sato. Tohoku J. Exper. Med. 68:303 (25 Oct.), 1958.

The results demonstrated that the bilirubin content in the gallbladder bile of dogs increased somewhat within two weeks after the papilla of Vater had been stimulated and secondary dyskinesia had been induced. This seemed to increase gradually over a one-month period. In those cases in which infection and stasis had been caused in the biliary tract by the introduction of ascaris egg suspension and the application of a loose ligature of the cystic duct, the decrease of the bilirubin content was rapid, viz. within one week. The color of the bile also changed into a greenish brown on this occasion, and it was lower in its viscosity.

In Report II, the author described that the bilirubin content in various kinds of pathologic human bile is much less than that of healthy human bile. In the present study, it has been confirmed that a similar tendency is shown in the pathologic dog's bile. It has been proved through this animal experiment that the stasis and infection of the biliary tract will accelerate the lessening of the bilirubin content in the bile of the dog.

MORTON SCHWARTZ

STUDIES ON BILE PIGMENT IN BILE. IV. EXPERIMENTAL STUDY ON BILIRUBIN CONTENT OF BILE IN DOGS FED ON HIGH OR LOW PROTEIN: Tomonobu Sato. Tohoku J. Exper. Med. 68:309 (25 Oct.), 1958.

The gallbladder bile obtained from the dogs of low protein feeding group was almost the same in appearance as from the dogs of high protein feeding group, and the difference between the two could be hardly distinguished in color and viscosity. But the comparison of the two results given above showed a marked difference in the bilirubin content in the bile.

It was noted that the bilirubin content in the bile of a dog fed on a high protein diet was higher than that fed on a low protein diet. From the experimentation performed by the author it was surmised that the difference in bilirubin in the bile of the Japanese as compared with the Caucasian was probably not due to anything more than the concentration of protein ingested in the respective diets.

MORTON SCHWARTZ

THE SURGICAL PATIENT: ORAL BOUILLON FEEDINGS: H. B. Benjamin, Marvin Wagner, Nunilo L. Bugarin and Gretchen Bartenbach. J. Internat. Coll. Surgeons 30:405 (Oct.), 1958.

All surgeons agree that following any type of surgery special care must be given postoperatively. The author feels too much stress is placed on intravenous infusions to maintain electrolyte and nitrogen balance. This is time-consuming and only after considerable calculating does one ultimately arrive at a suitable formula of nutrients for a specific patient. The author feels that the simple approach would be to feed the patient by mouth foods that could be tolerated. To this end he experimented with various broths and describes how he finally determined upon Nestlé's Beef Broth. This was used in conjunction with regular electrolyte therapy. The paper includes

charts showing the blood chemistry of the patients and comparable charts on bouillon therapy and electrolyte therapy. It is an interesting paper and one should keep this type of postoperative care in mind.

ABRAHAM BERNSTEIN

EFFECT OF ALUMINUM HYDROXIDE ON THE INTESTINAL ABSORPTION OF CHLORAMPHENICOL: Teruo Takasu, Louis Bosco, Bernard J. Clark and Howard W. Marraro. New England J. Med. 259:767 (16 Oct.), 1958.

According to Weinberg "Chloramphenicol is not usually considered to be affected by metallic ions". The authors attempted to determine whether adequate blood levels of chloramphenicol could be obtained if the patient was simultaneously ingesting aluminum hydroxide gel. In this series a limited number of patients (6) were utilized and their studies indicate that the Chloramphenicol blood levels are not affected by the simultaneous ingestion of aluminum hydroxide gel. Incidentally, they also observed that the presence or absence of free gastric juices did not affect the absorption of chloramphenicol. These observations bear out the theoric conclusion reached by biochemists and pharmacologists that chloramphenicol does not readily *chelate*.

IRVIN DEUTSCH

TREATMENT OF ULCERATIVE COLITIS WITH TOPICAL HYDROCORTISONE HEMISUCCINATE SODIUM: Geoffrey Watkinson. Brit. M. J. 5104:1077 (1 Nov.), 1958.

The author has assessed the value of rectal instillations of topical hydrocortisone hemisuccinate sodium in patients with ulcerative colitis. In comparison with the control group receiving an inert preparation the majority of patients receiving potent hydrocortisone improved and those receiving inert therapy worsened. In two patients who served as their own controls, dummy treatment failed to induce improvement while hydrocortisone caused a remission to occur. Comparison by sequential analysis showed that symptomatic remission and improvement in mucosal appearances were significantly more often induced by potent than by inert treatment.

JOHN M. MCMAHON

TREATMENT OF ULCERATIVE COLITIS WITH LOCAL HYDROCORTISONE HEMISUCCINATE SODIUM: S. C. Truelove. Brit. M. J. 5104:1072 (1 Nov.), 1958.

The author has made an extensive evaluation to show whether topical hydrocortisone hemisuccinate sodium has a genuine beneficial action in ulcerative colitis. At the end of one week of treatment the patients receiving this preparation showed a striking advantage over those on an inert preparation; not only in respect to clinical improvement but also in regard to the sigmoidoscopic appearance and the histologic condition of colonic biopsy specimens. All patients were then given open therapy with topical hydrocortisone and antibiotics used in conjunction for 2 weeks. The addition of antibiotics seems to confer a small gain in the number of successes with topical hydrocortisone therapy although a few patients developed exacerbation of symptoms.

JOHN M. MCMAHON

RELATION OF AZOTEMIA OF BLOOD "AMMONIUM" IN PATIENTS WITH HEPATIC CIRRHOSIS: Leslie T. Webster Jr., George J. Gabuzda. A.M.A. Arch. Int. Med. 103:15 (Jan.), 1959.

Arterial blood ammonium concentration in a group of patients with azotemia was normal. These persons had a normal liver function and were contrasted with another group having azotemia and hepatic disorders. Each patient with liver dysfunction and azotemia showed also an elevated blood ammonium. These findings were interpreted to mean that increased blood urea may contribute to the elevation of blood

ammonium in the presence of hepatic disease. The blood urea nitrogen substances may enter the gastrointestinal tract and be broken down there by bacteria. Hereafter, the resulting ammonium may be reabsorbed in the portal circulation. If this mechanism was operating the effect of neomycin in hepatic coma would be a suppression of bacterial ammonia formation in the gastrointestinal tract. In order to prove this hypothesis the nitrogen contents of the gastrointestinal tract was determined before and after neomycin. Neomycin produced not only a decrease of the blood ammonium but also an increase of the nitrogen substances in the gastrointestinal tract indicating that it blocked the bacterial urease activity. Sudden renal dysfunction with azotemia may precipitate hepatic coma in persons with severe hepatic disease.

H. B. EISENSTADT

DETERMINATION OF CARDIOPORTAL CIRCULATION TIME BY EXTERNAL SCINTILLATION COUNTING: Ismael Mena, Leslie R. Bennett, Raymond Kivel, Joseph Scallon, Sherman M. Mellinkoff. Am. J. Digest. Dis. 4:19-28 (Jan.), 1959.

The paper introduces a new technic utilizing radio-iodinated human serum albumin and externally placed scintillation counters. The method, simple and safe, showed results corresponding with known alterations in hepatic hemodynamics. The portal circulation time is increased in cirrhosis and appears to reflect the portal pressure. It was found to be drastically changed in seven patients with cirrhosis who had undergone portacaval anastomosis. The method may turn out to be a valuable diagnostic aid like for instance in gastric hemorrhage to rule out esophageal varices.

WALTER CANE

SERUM VITAMIN B_{12} CONTENT IN LIVER DISEASE: Thomas D. Stevenson and Marion F. Beard. New England J. Med. 260:206 (29 Jan.), 1959.

The serum content of Vitamin B_{12} as determined by microbiologic assay increased with progression of liver disease in patients with cirrhosis or hepatitis, and decreased toward normal coincident with improvement. The highest levels were found in hepatic coma. In cases with obstructive jaundice the serum Vitamin B_{12} level was within normal limits. The mechanism of the increased serum level was investigated by means of radioactive Vitamin B_{12}. Absorption, excretion, and plasma clearance were within the normal range. Therefore the increased serum Vitamin B_{12} content in hepatic disease was considered to be due to release of the vitamin from the liver as the result of hepatocellular necrosis. The determination is too cumbersome and is not to be recommended as a test of hepatic function.

ERNEST LEHMAN

TREATMENT OF TRICHURIASIS WITH DITHIAZANINE: D. H. D. Paine, E. S. Lower and T. V. Cooper. Brit. M. J. 5114:93 (10 Jan.), 1959.

The results of six cases of trichuriasis treated with dithiazanine is reported with favorable results. The total daily dosage was 600 mg. given as 100 mg. tablets three times daily regardless of weight and age for five days.

The antihelmintic effects of the cyanine dyes, dithiazanine in particular, appears to reside in their ability to interfere with oxygen uptake and carbohydrate metabolism.

The adult worms were usually found in the stool from three to five days after the beginning of treatment. They were in a motile, dead state.

As with the experience of Swartzwelder et al (1957) with 400 patients, this series noted that the only reactions observed were vomiting and diarrhea. Associated conditions as pregnancy, anemia, nephrosis, etc. did not alter the tolerance to the drug.

EZRA J. EPSTEIN

A SIX-MONTH EVALUATION OF AN ANABOLIC DRUG, NORETHANDROLONE, IN UNDERWEIGHT PERSONS; II. BROMSULPHALEIN (BSP) RETENTION AND LIVER FUNCTION: R. C. Kory, M. H. Bradley, R. N. Watson, R. Callahan and B. J. Peters. Am. J. Med. 26:243 (Feb.), 1959.

Abnormal BSP retention was found in 74 per cent of 47 subjects who received norethandrolone in order to induce weight gain.

Liver function studies were normal in all but two of the subjects who showed slight elevation of serum bilirubins and serum alkaline phosphatase. These returned to normal several weeks after stopping the drug.

No clinical evidence of liver dysfunction could be obtained in any of the subjects.

Of the seven liver biopsies obtained, four showed minimal abnormalities consisting of increased nuclear activity and slight to moderate infiltration of lymphocytes. One of these showed minimal focal necrosis and minimal bile stasis. The remaining three biopsy specimens had a normal histologic appearance.

A short-term study in ten geriatric patients indicated that a 25 mg. daily dose would result in abnormalities of BSP and SGOT in two to three weeks. The 50 mg. daily dose results in similar abnormalities after only one week.

It is considered probable that norethandrolone inhibits the transfer of BSP from the blood into the bile.

The mild and reversible nature of the liver dysfunction suggests that the drug in low dosage may be safely employed as an anabolic agent, even for long term therapy.

JOHN M. MCMAHON

BOOK REVIEWS FOR GASTROENTEROLOGISTS

1958-1959 YEAR BOOK OF ENDOCRINOLOGY: Gilbert G. Gordan, M.D., Ph.D., F.A.C.P., Associate Professor of Medicine, Chief of Endocrine Clinics, Department of Medicine, University of California School of Medicine, Associate Physician, University of California Hospital, Assistant Visiting Physician, San Francisco Hospital, San Francisco, Calif. 384 pages, illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1959. Price $7.50.

As in previous editions, the staff of the Year Book of Endocrinology abstracted the most important articles from the medical literature deaing with this subject. The editor was fortunate to have the cooperation of his many colleagues interested in endocrinology and allied subjects.

This well written and illustrated book is highly recommended to physicians and research workers.

CIBA FOUNDATION SYMPOSIUM ON CARCINOGENESIS—MECHANISM OF ACTION: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Maeve O'Connor, B.A., Editors for the Ciba Foundation. 336 pages, 48 illustrations. Little, Brown & Co., Boston, Mass., 1959. Price $9.50.

One of the most interesting chapters in the book, page 12, calls attention to the accidental discovery by the late Dr. Oppenheimer, a New York physician, who with Mrs. Oppenheimer, while studying the production of hypertension in the rat, investing the kidney with cellophan to induce it, unexpectedly noted the development of sarcomata in relation to the cellophan sheets. Further discussions of this observation bring to light the possibility of cancer-producing substances which inadvertently may produce carcinogenic lesions.

It is recommended that all those who are interested in solving the cancer problem will greatly benefit from reading this interesting symposium.

CANCER AND ALLIED DISEASES OF INFANCY AND CHILDHOOD: Irving M. Ariel, M.D., Associate Professor of Clinical Surgery, New York Medical College, Attending Surgeon, Hospital for Joint Diseases, Staff Surgeon, Long Island Jewish Hospital, Attending Surgeon, Pack Medical Group, New York, N. Y. and George T. Pack, M.D., Associate Professor of Clinical Surgery, Cornell University Medical College, Attending Surgeon, Memorial Center for Cancer and Allied Diseases, Attending Surgeon, Pack Medical Group, New York, N. Y. Twenty-seven contributing authors. 605 pages, illustrated. Little, Brown & Company, Boston, Mass., 1960. Price $22.50.

Under the able editors, Ariel and Pack and the 27 contributing authors, Little, Brown & Company have given to the medical profession an unusually comprehensive and timely volume dealing with cancer and allied diseases of infancy and childhood. It is fascinating reading, the illustrations and the explanations accompanying them, should be read and reread by all physicians whether or not they specialize in pediatrics.

Leukemia and lymphomas in childhood, plus cancer of the gastrointestinal tract, pancreas, liver and heart, are of great interest as these conditions are often overlooked.

Extensive bibliography and index complete the text.

It is highly recommended as a valuable addition to the doctor's library.

RONTGENDIAGNOSTIK DES MAGEN-DARMKANALS: Prof. Dr. R. Prevot, Hamburg and Priv.-Doz. Dr. M. A. Lassrich, Hamburg, 346 pages, 544 illustrations. Georg Thieme Verlag, Stuttgart, Germany, 1959. Price $28.80.

An excellent volume, clear and concise. One who has some knowledge of interpreting roentgen films, will find many unusual and interesting photographs of normal and abnormal gastrointestinal conditions.

Translation into English and other languages is recommended by the reviewer.

A WAY OF LIFE AND OTHER SELECTED WRITINGS OF SIR WILLIAM OSLER: with an introduction by G. L. Keynes, M.D., F.R.C.S. 278 pages, illustrated. Dover Publications, Inc. New York, N. Y., 1958. Price $1.50.

Although these writings first appeared in 1951 as "Selected Writings of Sir William Osler" and published by the Oxford University Press, the present edition, unabridged and unaltered, was republished in 1958.

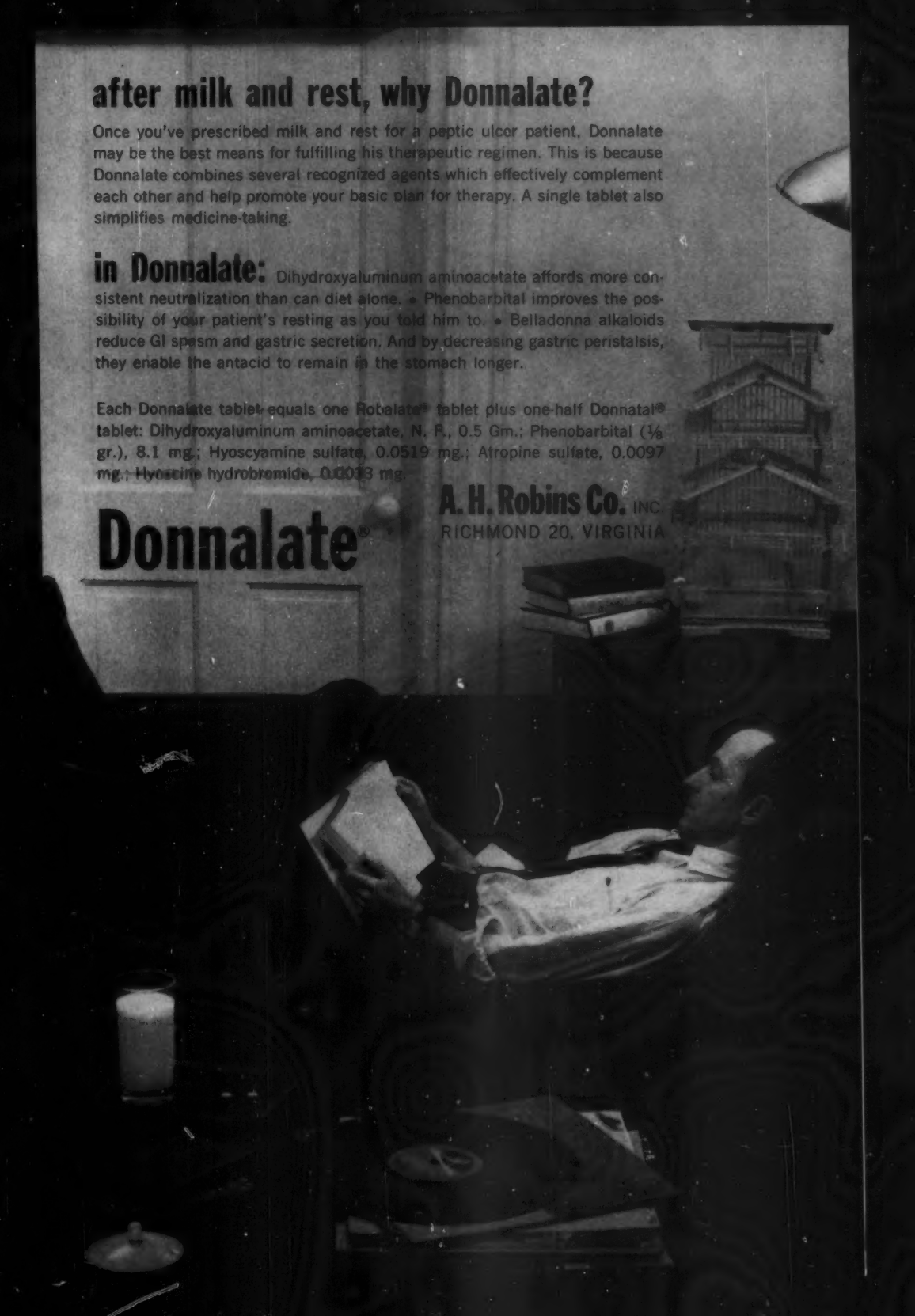
It is recommended that the medical student read these selections and acquaint himself with Osler, the man.

RADIOISOTOPE STUDIES OF FATTY ACID METABOLISM—VOLUME I: James F. Mead and David R. Hawton, Department of Laboratories of Nuclear Medicine and Radiation Biology, University of California, Los Angeles, Calif. Another Monograph of the International Series on Nuclear Energy: R. A. Charpie and J. V. Dunworth, General Editors. 141 pages. Pergamon Press, New York N. Y., 1960. Price $7.50.

Research workers in the lipid field will find important material in this monograph. The most important of these tracer elements is the long-lived radioactive carbon isotope. Previously, biochemists demonstrated that fats of the body are not the inert storage substances they were originally presumed to be.

The field of fatty acid biochemistry is reviewed concisely and the student of biochemistry will profit by the information brought together for the first time.

An author's and subject index complete the book.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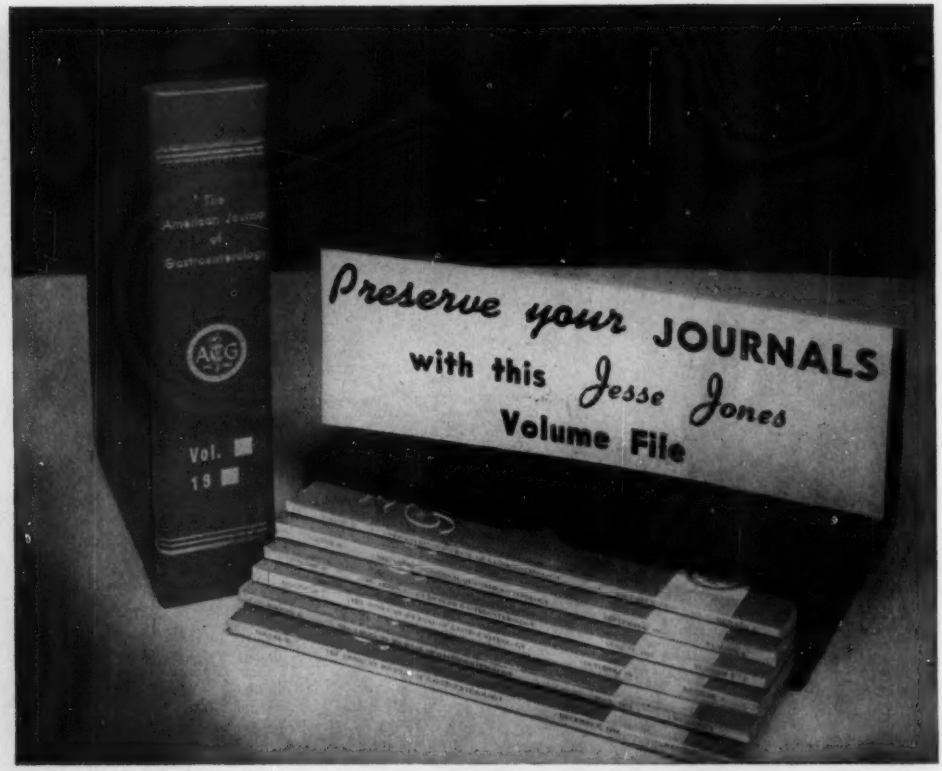

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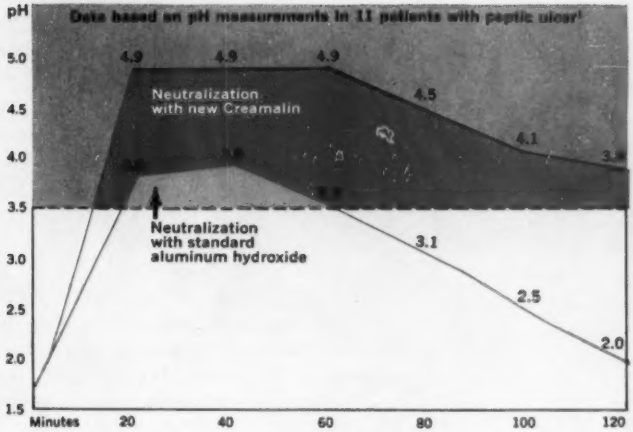

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Each new Creamalin antacid tablet contains 320 mg. of specially processed, highly reactive, short polymer dried aluminum hydroxide gel (stabilized with hexitol) with 75 mg. of magnesium hydroxide. Minute particles of the powder offer a vastly increased surface area for quicker and more complete acid neutralization.

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1. Data in the files of the Department of Medical Research, Winthrop Laboratories. 2. Hinkel, E. T., Jr.; Fisher, M. P., and Tainter, M. L.: J. Am. Pharm. A. (Scient. Ed.) 48:384, July, 1959.

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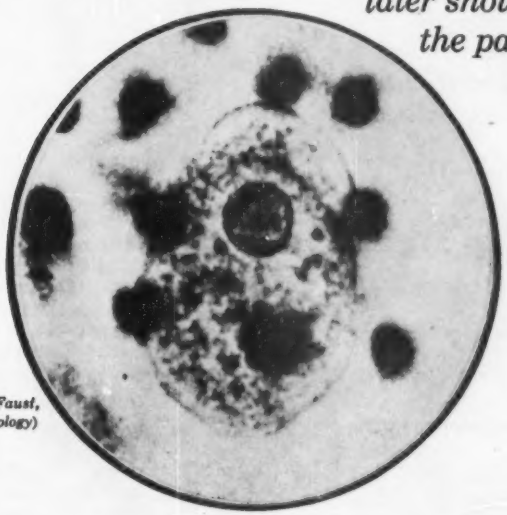

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RESULTS OF POST-TREATMENT STOOL EXAMINATIONS FOR E. HISTOLYTICA

No. of Patients Examined	No. of Controls	No. Positive Before Treatment	No. Positive After First Course of Treatment
135	26	23	2

8 DAYS OF TREATMENT RESULTS IN 90% CURES

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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). Am. J. Gastroenterol. **34**:429-432 (Oct.), 1950.

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orien in der Chirurgie, Med. Klin. 49:1921-22, 1954. 53. Millack, J.: Obstipationstherapie waehrend der Graviditaet 'raxis 9/6: (Feb.) 1957. 54. Moreton, R. D.: The roentgenologic examination of the colon, presented at the Annua of the American Roentgen Ray Soc., Wash., D.C., Oct. 1, 1 . 55. Ohlms A. C.: Rektale Anwendung von Laxantien ische 22:819-821, 1955. 56. Pincock, J. G.: The use of a rectal suppository of bisacodyl (Dulcolax) in geriatric patients M.A.J. 82:268-269 (Jan. 30) 1960. 57. Poppel, M. H.: Bowel preparation for radiologic procedures using a new evacuant l, Am. J. Roentgenol. 81:696-699 (Apr.) 1959. 58. Rashin, H. F., Palmer, W. L., and Kirsner, J. B.: Exfoliative cytolog osis of cancer of the colon, Dis. Colon & Rectum 2:46-57 (Jan.-Feb.) 1959. 59. Raymond, O.; Nogrady, B., and Vézina ffective evacuation of the colon by a new therapeutic agent, bisacodyl, proven in radiology, Scien. Exhibit presented at the 22nd Meeting of the Canadian Assoc. of Radiologists, Saskatoon, Sask., Canada, 1959. Raymond, O., Nogrady, B., and Vézina ffective evacuation of the colon by a new therapeutic agent, bisacodyl, proven in radiology, Canad. M.A.J. 82:1077-8) 1960. 61. Roth, F.: Dulcolax als Klysma-Ersatz in der Geburtshilfe und Frauenheilkunde, Ther. Umschau, Bern 15:55-5 1958. 62. Rutter, A. G.: Bisacodyl; an evacuant drug, Lancet 1:1213-14 (June 6) 1959. 63. Sánchez Capelot, Francisco chez Martin, Agustin: Experimentacion clinica con el laxante [illegible]to. Med. espan. (Valencia) 36:372-376 (Nov.) .. Schaal, W., und Bachor, W.: Erfahrungen mit [illegible]-Diacetoxy-diphenyl)- [illegible]-äthan—einem neuen Kontakt Med. klin. 48:1072-73, 1952. 65. Schaal, W., und Bachor, W.: Erfahrungen mit (4,4'-Diacetoxy-diphenyl)-(pyridyl-2) -einem neuen Kontakt-Laxans, Med. klin. 48:1051-52 (Dez. 26) 1953. 66. Schaal, W.: Erfahrungen mit einem neuer laxativum in einer indischen Praxis, Hippokrates 26:623-625, [illegible] Zwergel, D.: Darstellung der Kolonschleimhau ilitaetspruefung des Dickdarmes mit Hilfe verschiedener Kontaktlaxantien, Klin. Wschschr. 12:533-536, 1934. 68. Schmidt Berger, E.: Geriatrische Erfahrungen mit Dulcolax, [illegible]ien. med. Wschr (Mar. 29) 1958. 69. Schmidt, L.: Pharmakologie und Toxikologie einer neuen Klasse von Verbindungen mit laxierende t, Arzneimittel-Forsch. 3:19-23, 1953. 70. Schmidt, L., und Sorger, E.: Die pharmakologische Wirkung synthetische n in Beziehung zu ihrer chemischen Konstitution, Arzneimittel-Forsch. 6:[illegible]-26 (Jan.) 1957. 71. Schoenemann, C. B. l (Dulcolax) as a postoperative laxative, Canad. M.A.J. 81:128 (July 15) 1959. 72. Schultz, E., und Thoenelt, K. Ver ng der Vorbereitung und Verbesserung der Methodik beim Kontrastdarmeinlauf durch Anwendung eines Kontakt ns, Med. Welt [illegible]63, 1960. 73. Schultz, O. E., und Schnekenburger, J.: Chemische Konstitution und pharmako Wirkung der Laxantien unter besonderer Berücksichtigung von Verbindungen mit zwei p-oxyphenyl-Gruppen an einen imen Kohlenstoffatom. 3., Arch. Pharm., Berl. 291/63:356-361 (July) 1958. 74. Schultz, O. E., und Schnekenburger, J. ie Konstitution und pharmakologische Wirkung der Laxantien unter besonderer Berücksichtigung von Verbindungen mi oxyphenyl-Gruppen an einem gemeinsamen Kohlenstoffatom. 4., Arch. Pharm., Berl. 291/63:369-[illegible] (July) 1958. 75 hn E. S.: A new laxative, Practitioner 177:615 (Nov.) 1956. 76. Sokolow, Jack: Preliminary report on the clinical use o xative, Clin. Med. 5:1195-96, 1198 (Sept.) 1958. 77. Sowerbutts, T. G.: Hazards of water enemas (Letter to the Editor) '079:944 (May 2) 1959. 78. Stahel, R., und Kyburz, O.: Erfahrungen mit Ri[illegible], Praxis [illegible]:221-222 (Feb. 27) 1958 npfli, F.: Ueber die Behandlung der Obstipation von Hysterikern die mit Ganglienblockern behandelt wurden, Ther 2, Bern 15:10, 1958. 80. Stasny, K.: Die Behandlung der chronischen Obstipation im Alter, Wien. med. Wchnschr 718, 1957. 81. Stockmeier, Fritz: Erste Erfahrungen mit einem neuen Kontaktlaxativum, München. med. Wchnschr 60, 1953. 82. Vieth, Herbert: Klinische Erfahrungen in der Kontaktlaxantienbehandlung der [illegible]. Tbc mit einem neuer axativum. Ther. D. Gegenw. [illegible]:62, 1955. 83. Wayand, E., und Schwanzer, H.: Erfahrungsbericht ueber die Ver des Kontaktlaxativums La 964 bei abdominalchirurgischen Patienten, Klin. med. [illegible]:295-296, 1957. 84. Weihs, E.: Kli eobachtungen und Erfahrungen bei der Behandlung der Obstipation in der Psychiatrie unter Anwendung eines neuer laxativums ("Laxans Thomae"), Fortschr. Med. 76:27-28, 1958. 85. Weiss, Jerome: Constipation; newer trends in treat m. J. Proct. 11:111-121 (Apr.) 1960. 86. Zettel, G.: Die Darmentleerung als vorbereitende Massnahme f. Röntgenuntersuch h des Abdomens, Ther. Gegenw. 96:337-338 (Sept.) 1957. 87. Zimmermann, M.: Unsere Erfahrungen mit der Curare-Lachgas bei gynaekologischen Operationen, Aerztl. Wchnschr. 9:540-544, 1954. 88. Zimmermann, H.: Die Verwendung von Kon

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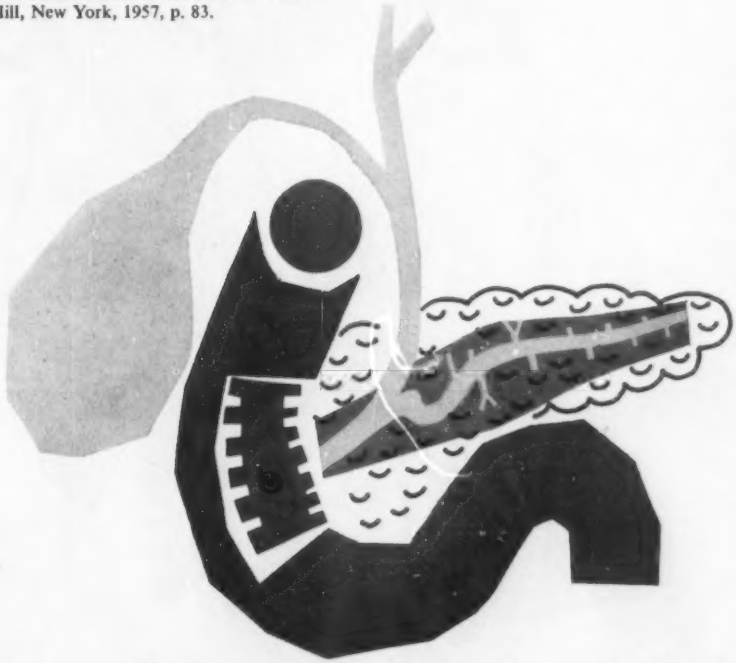
Source: Popper, H., and Schaffner, F.: Liver: Structure and Function, McGraw-Hill, New York, 1957, p. 83.



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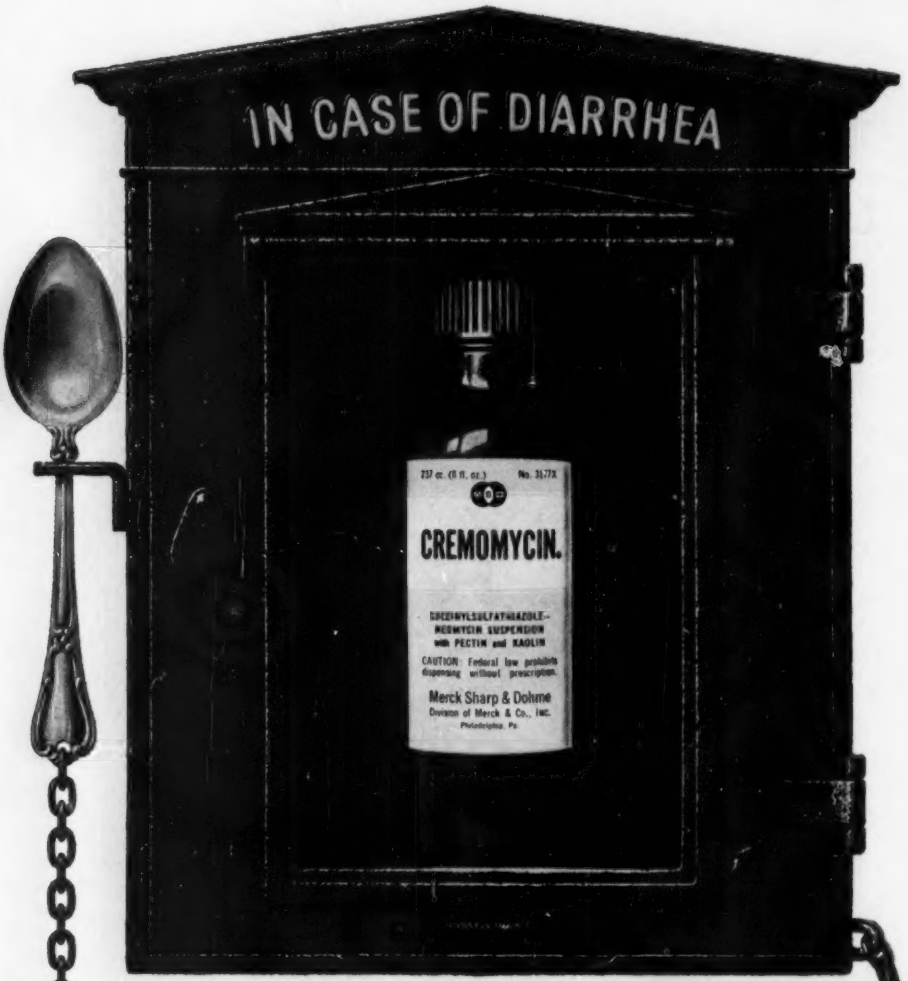

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